



The Complex Case for Another Hard Look

Transnational Pharmaceutical Regulation and the Pedagogical Role of Courts

Marco Rizzi

Thesis submitted for assessment with a view to obtaining
the degree of Doctor of Laws of the European University Institute

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Department of Law

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ABSTRACT

The thesis argues for a ‘pedagogical’ role for courts in the US and EU in ameliorating the increasingly transnational regulation of pharmaceutical product safety through complementary monitoring of the outputs of regulatory processes. The study is divided into two parts.

First, the thesis explores the regulatory institutional design in the US and EU. The parallel development of the FDA and EMA suggests that both markets have achieved consolidated domestic/regional regulatory frameworks, which do however show multiple weak spots. These vulnerabilities are aggravated by a strong push towards transnationalisation of regulatory procedures: domestic systems are now permeated by potentially disruptive exogenous elements (e.g. the ratification of transnationally negotiated protocols and increasing reliance on foreign clinical trials data). The thesis explores issues of effectiveness of safety delivery and legitimacy of rule-making processes to suggest scope for improvement in both areas.

The second part considers the potential contribution of the judiciary, particularly national courts in the US and EU, to investigate whether the exercise of complementary judicial governance can enhance the effectiveness and legitimacy of an otherwise essentially closed and self-perpetuating system. A selection of cases grounds the claim that, through liability litigation, courts have the capacity to improve the safety levels delivered by regulation and thereby to contribute to output-based legitimacy of the institutional design. This claim is tested in light of acknowledged strengths and limitations of court processes and with regard to differentiating elements at the national level, particularly regarding access to justice.

The concluding argument reassembles the results of the study to recommend the existing tool of domestic litigation as a response to certain vulnerabilities in pharmaceutical regulation. The ‘hard look’ doctrine described by Sheila Jasanoff grounds the normative claim for a ‘pedagogical’ role for courts, enhancing regulation beyond the outcome of isolated cases – *ad adiuvandum* rather than *contra*.

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“That’s the thing about sailing...you gotta deal with it!”

[A worldly seaman, somewhere in the Indian Ocean]

The journey approaches its end, and looking back at the long incredible years that led to this moment is a truly emotional exercise. I have taken this thesis with me across four continents, countless countries, capitals, provinces, ports and country villages. As I sit to reassemble those memories and acknowledge those who traveled with me I can only picture a long and difficult sailing race, a regatta. One requiring the strongest equipment, loving maintenance, friendly ports, a trusted crew and the guidance of shining stars. The sailing can be (as it has been) hard, discouraging, scary, but also thrilling, fun and exhilarating. And nothing, really nothing, matches the feeling of gazing at the horizon and yelling from the top of your lungs “LAND HO!” - We made it! Yes, ‘we’, because one does not get to port on his own.

First, I need to thank, wholeheartedly so, my supervisor Professor Hans-Wolfgang Micklitz. If I have sailed so far I owe it to his patience, his support and his steady but never invasive guidance. My gratitude to him is both of an academic and personal nature, because no matter how badly the boat gets lost in a storm, or how much it drifts off when the wind dies, a compass will always show the right course. I will miss having him as my compass in the years to come. I can only hope I have learned enough to navigate on my own. You surely taught me well.

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A spinnaker is a complicated sail, hard to maneuver, and it only really works on one board. Yet, when you manage to catch that good downwind gust, there is nothing like the '*spi*' to make you fly. Caterina, Carlotta, Angelo, Pino, Pippo, Federico: unfortunately we haven't seen each other very often in these last years, really not enough. But with the spontaneity of our occasional encounters, the richness, personal and intellectual, of our exchanges, the sheer happiness of being together when we could, you gave me incredible boosts. Often at times when I needed them the most. Often without you even knowing it.

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Karolina, Lena, Igor, Laura, Daria, Pietro, Caterina, Punky (and the burgers). But how could I not mention the great teams I had the absolute privilege to play and compete with? The 'Amici del Nuoto', motley bunch of chlorine addicts. The inimitable 'TUE Calcio – Squadra Fantastica' - our run to the B2 AICS title will always be one of my all-times highlights. The brotherhood of the 'Montecarla Spettacolo'... Thank you! For all the magic, for everything!

The most trusted friends of a sailor are the stars. When everything else works, they confirm all is well. When everything else fails, they guide you back to course. No matter what, they will always be there, and unfortunately I do not possess adequate words to express how grateful I am to my stars.

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“Noi non possiamo essere imparziali. Possiamo essere soltanto intellettualmente onesti: cioè renderci conto delle nostre passioni, tenerci in guardia contro di esse e mettere in guardia i nostri lettori contro i pericoli della nostra parzialità. L'imparzialità è un sogno, la probità è un dovere.”

Gaetano Salvemini, *Mussolini Diplomatico*

“La recherche en sciences sociales est et sera toujours balbutiante et imparfaite. Elle n'a pas la prétention de transformer l'économie, la sociologie et l'histoire en sciences exactes. Mais en établissant patiemment des faits et des régularités, et en analysant sereinement les mécanismes économiques, sociaux, politiques, susceptibles d'en rendre compte, elle peut faire en sorte que le débat démocratique soit mieux informé et se focalise sur les bonnes questions. Elle peut contribuer à redéfinir sans cesse les termes du débat, à démasquer les certitudes toutes faites et les impostures, à tout remettre toujours en cause et en question.”

Thomas Piketty, *Le Capital au XXI^e Siècle*

“Our society is not committed to preserving life at any cost [...] lives are spent not only when the quid pro quo is some great moral principle, but also when it is a matter of convenience.”

Guido Calabresi, *The Costs of Accidents*

INTRODUCTION

The fundamental question inspiring this work is whether the risk regulation regime for pharmaceutical products is beset with fundamental problems which, when globally considered, include issues of consumer protection. The reasons for raising this question are manifold, but in sum they stem from the observation that the state-based and centralised, top-down, law-making/enforcement model of pharmaceutical safety regulation elaborated throughout the 20th century is confronted with disruptive factors aggravating its inherent difficulties. At present the pharmaceutical market exhibits significant traits of what can be defined as a *closed and self-perpetuating system*, pre-eminently oriented towards demand for rapid access to markets. This work explores both the nature and extent of ensuing consumer safety issues, and the possibility for courts to provide a form of complementary oversight and perform a ‘pedagogical’ role in the improvement of regulatory schemes.

A quick snapshot of the major issues at stake serves to clarify the reasons leading to the research question on the state of pharmaceutical safety. Taking as an analytical standpoint recent conclusions of statecraft to the effect that the function of the State has switched from welfare provision (in the form known as the “nation state”) to maximising economic opportunities (in the most recent form of the “market state”),¹ the functioning of and balance between pre-marketing assessment and post-marketing management need to be reconsidered in their essence. What will be investigated here is how this market state shift is affecting pharmaceutical safety and what potential role exists for courts in strengthening the legitimacy and effectiveness of risk regulation.

The first part of the thesis focuses on the system of governance for pharmaceutical safety that has been constructed in the course of the 20th century around

¹ Bobbitt P., *The Shield of Achilles – War, Peace and the Course of History*, KNOPF, 2002, p. 229, explaining that “[s]uch a State depends on the international capital markets and, to a lesser degree, on the modern multinational business network to create stability in the world economy, in preference to management by national or transnational political bodies [...] Whereas the nation-state justified itself as an instrument to serve the welfare of the people (the nation), the market-state exists to maximize the opportunities enjoyed by all members of society”: and p. 230, expanding on its defining characteristics, “...the market state is largely indifferent to the norms of justice, or for that matter to any particular set of moral values so long as law does not act as an impediment to economic competition”.

national (or regional as in the EU) centralised agencies, with a primary focus on the pre-market assessment of new products, and a subsidiary one (at first, but progressively more prominent) on post-marketing surveillance (with the development of the *pharmacovigilance* system). The limited resources of these agencies are very much concentrated on the domestic markets in which they exercise authority.

The thesis provides an overview of the historical development of the two agencies in charge of marketing approval procedures for pharmaceutical products in the two markets where over 80% of worldwide products are distributed and consumed: the FDA and the EMA. This is a meaningful exercise in order to refine the understanding of, on the one hand, how difficult transnational regulatory harmonisation processes are, and, on the other, how problematic transnational regulatory practice can be. The separate historical development of the FDA and the EMA has led to the establishment and consolidation of institutions with substantially different characteristics, despite the fact that they are often treated as equivalents in practice. The widespread use of mutual recognition agreements between the US and the EU in pharmaceutical regulatory matters calls for an attentive look at the extent of divergence between two bodies that have been exchanging data for at least two decades, and are expected to move towards ever-closer cooperation.

The analysis of the development of both the FDA and the EMA attempts to expose three fundamental phases in the evolution of pharmaceutical regulation. The first phase is the acquisition of ever-greater independence by such agencies and what can be referred to as ‘bodies of expertise’ *vis à vis* political institutions, both in the policy-making and in the decision-taking stages. The second phase, a direct result of the initial one, consists of the creation and consolidation of significant asymmetry between the formal distribution of power among political institutions and agencies, and its substantial exercise. While formally a great deal of decision and policy-making power remains within political institutions, the actual exercise of that power is fundamentally outsourced to agencies that organise themselves independently. The third phase is the shift to the global arena. Here the focus is on the dichotomy between the transnational nature of the regulatory process and the domestic design of the regulatory frameworks leading to marketing approval.

The pressure of globalised markets has deeply influenced this system of governance over the last two decades. The World Health Organisation (WHO), and

specifically the International Conference of Drugs Regulatory Authorities (ICDRA) forum, pointed out in the late 1980s the inadequacy of the monitoring-only role of the WHO in supervising international minimal standards of drug quality. Taking up the ICDRA's recommendation for a higher level of harmonisation, in 1990 the European Medicines Agency (EMA), the Food and Drug Administration of the United States (FDA), and Japan's Ministry of Health, together with relevant regional representatives of the pharmaceutical industry, created the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The institution of the ICH as a transnational regulatory body, where voluntary protocols and guidelines are directly negotiated by representatives of both the major regulatory agencies and the regional industry representatives, is tangible proof of the switch to a market state era. The guidelines produced are explicitly oriented towards a faster, more efficient, and less burdensome transnational market approval process, and they are regularly accepted and implemented by national agencies.

The practice of pre-market pharmaceutical regulation has accordingly gone transnational, although the only 'hard law' in place remains national or regional, and enforcement is essentially national. This, we submit, poses two sets of problems:

(1) The quality/relevance of the scientific knowledge emerging from the current regulatory framework requires a critical analysis. The institutional design with domestic agencies as key players is to be questioned on the basis of empirical data relating to the quality, provenance, and compatibility to receiving markets of scientific data resulting from outsourced clinical trials. This is because clinical tests on human subjects constitute the paramount and primary source of the scientific knowledge incorporated in risk assessment decisions about the marketing of new products. The presentation of said knowledge in foreign contexts, and its use in receiving markets, calls for an examination of its robustness. The third phase of regulatory evolution briefly sketched above involves the shift towards the global dimension of regulatory processes, which is problematised by the eminently domestic nature of current regulatory frameworks that remain fundamentally nationally or regionally rooted. The hypothesis is thus the following: strong domestic regulations can be vulnerable when permeated by exogenous factors that are not fully accounted for. Key questions include whether the absorption of foreign data still produces compliance with the goals of domestic regulation – that is, substantial and not merely

formal regulatory compliance. The thesis questions the effectiveness of these domestic systems with a description of the phenomenon of clinical trials outsourcing coupled with a series of critical elements suggestive of potential structural biases in data quality and reliability. The uncertain scenario the study confronts necessarily invites questions as to the quality of pre-market assessments.

Among the constitutive elements of this uncertainty lies the observation that, while transnational guidelines are regularly adopted by national regulators, their implementation is not entirely consistent. Moreover, if there is now substantial unanimity on procedural issues such as ‘good clinical’ and ‘good manufacturing’ practices, there is still a margin of disagreement on substantial issues such as the definitions of content and conduct of clinical trials. This means for instance that there is only basic agreement (in the form of minimum standards) on crucial choices regarding selection criteria for clinical trial populations, and/or the interpretation criteria, quality monitoring, and desired results of said trials. Are such divergences inherently liable to compromise the quality of scientific outcomes? As transnational regulatory practice for marketing approval involves an ever-increasing number of bodies across the world, working with incompletely harmonised (and nationally interpreted) regulatory rules and standards, there is room to suggest the existence of non-negligible levels of ambiguity in the quality of the emerging scientific knowledge. This hypothesis questions the very idea of ‘regulatory compliance’ in terms of adherence to the regulatory goals of a specific domestic legal framework. Procedurally, it is hardly debatable that any agency-approved drug complies with the relevant regulation (even in case of outsourcing of parts of the procedure to a different country). What is questionable is substantial compliance with the standards laid down by the regulator of the receiving market. It is important to underline that the idea of risk-benefit analysis is a grounding feature of both regulatory and litigation assessments, so that ambiguity of the data analysed may undermine the quality of the assessment itself.

(2) The second set of issues relates to the structure, nature, and impact of transnational guidelines, which call into question the legitimacy of pharmaceutical safety regulation and the accountability of the regulators. If regulators are shaping their policy around transnational guidelines explicitly oriented at expediting market access, there is a need to develop new forms of legitimacy/accountability to compensate for weakened traditional ones. Pharmaceutical safety, as the thesis discusses, is characterised by very

extensive delegation from the legislative to the executive branch. This poses legitimacy problems at a domestic level first, as the margin of discretion of executive-based agencies in both decision- and policy-making is such that genuine external oversight is limited. The evolution of pharmaceutical regulation throughout the 20th century shows a constant trend towards an ever-broader delegation to expert-based committees, operating within the framework of agencies more and more detached from legislators who appear to intervene almost exclusively in the wake of a crisis. The issue has been further complicated in the last 25 years by these executive agencies exercising their functions transnationally as negotiating actors. The thesis keeps questioning the domestically-shaped institutional design, shifting the focus to different and equally crucial aspects of the regulatory intricacies of pharmaceutical pre-marketing procedures. The magnitude of the clinical trials outsourcing phenomenon analysed in the thesis requires a discussion of the rules governing the use of foreign data by the FDA and the EMA, examining and questioning the provenance, law-making mechanisms, and sources of legitimacy of those rules, together with the accountability of the actors involved, in order to grasp the legal means by which strong national frameworks are permeated by exogenous elements.

The perspective remains coherent with the recalled division into three phases of regulatory evolution, and focuses specifically on the second and third phases – that is, on the one hand the asymmetry between formal distribution and effective exercise of power, and on the other hand, the dichotomy between domestic frameworks and global processes. Indeed, when discussing the origin and content of rules governing the use of foreign data, the effort centres on addressing their critical aspects in light of the major challenges they represent for domestically designed regulatory systems. It is accepted nowadays (especially in the European framework) that traditional modes of legitimation (that is, input-based democratic legitimacy) need to be revisited to meet the demands of multilevel governance of transnational phenomena. The theoretical justifications for the progressive abandonment of democratic legitimacy will be discussed insofar as they apply to the pharmaceutical sector. In a nutshell, in the current circumstances characterising the pharmaceutical market, legitimacy issues can be tackled in two different ways. One either takes a traditional approach, deriving from theories of democracy and representation, in which case the current setup presents major shortcomings. Or one could think of different forms of legitimacy in the form of either ‘deliberative’ (which maintains the

focus on the law-making stage) or output-based, rather than more consolidated input-based, mechanisms – in which case the question is whether the output of the current regulatory framework can be considered legitimate in terms of the effective delivery of its proclaimed goals. The latter is the approach with stronger support in the literature of pharmaceutical regulation – a position requiring discussion in light of the uncertainties suggested above regarding data quality and provenance.

What the thesis ventures upon is therefore an analysis of the ‘output’ of the system, and more specifically its output in terms of consumer protection and safety. A selection of case studies is necessary to investigate whether there are deficiencies in pre-marketing regulation hindering the goal of product safety, and whether post-marketing management and surveillance systems as provided by the current regulatory frameworks are sufficient to overcome the suggested issues of uncertainty in approval procedures and ‘democratic deficit’. The thesis maintains a complementary perspective that interprets the safety outcome as a sum of the pre-marketing results and the effectiveness of post-marketing reactive measures when a medicine causes unexpected adverse reactions (ADRs). Specifically the ‘outcome issue’ is broken down into a series of major sub-aspects: first, the structural fitness of pre-market rules to allow the emergence of assessment-relevant knowledge, and conversely the ability of post-marketing surveillance duties to uncover and react to supervening risk discoveries; second, the efficacy and timeliness of the system’s ‘reaction time’ when confronted with ADRs; and third, the existence of safer therapeutic alternatives present in the market. Interestingly, the cases show that (as recalled above) it is in the presence of a crisis situation that the national legislator recuperates its original function. The thesis however argues that such national reactions appear to be unfit to confront the transnational dimension of the pharmaceutical market.

In sum, the two major sets of issues identified in **(1)** and **(2)** pose the fundamental question: to what extent is procedure affecting substance?

We have suggested in the opening that, as currently designed, the pharmaceutical safety regime with its transnational *tournure* exhibits traits of what can be defined as a *closed and self-perpetuating system*, very much oriented towards the trade necessity of overriding obstacles to the free flow of products, and towards rapid access to markets. After analysing the regulatory dimension of pharmaceutical safety and underlining some of its

critical features, the thesis then turns to the lens of the judiciary in pharmaceutical safety, with a view to developing the premises of a normative claim for the complementary role of courts. Specifically, the argument posits that courts have the potential to contribute substantially in bringing balance to the market orientation of the pharmaceutical *closed and self-perpetuating system*, by helping to clarify the quality and nature of scientific data, and by breaking the closure of the regulatory architecture through the introduction of exogenous and bottom-up challenges. The fundamental idea of the ‘hard look doctrine’, according to which courts can have a pedagogical role in the development and refinement of regulatory processes, inspires the second part of the work dedicated to the judiciary, and forms the theoretical basis of the concluding normative proposition.

As the first part of the thesis begins with an overview of the institutional design of Western pharmaceutical regulation, the second part opens with a similar descriptive account of EU and US courts’ involvement in the field. The most prominent role of courts in pharmaceutical regulation is to adjudicate tort claims in product liability suits. The analysis accordingly builds from the starting point of product liability law, discussing the development of its rules and practice in the selected markets when confronted with pharmaceutical cases. The focus is initially on two essential dimensions of product liability: the issues of foreseeability of risk (which relates to the notion of defect and in particular the available scientific knowledge to assess a product’s safety) and compliance with regulatory requirements.

Foreseeability, defectiveness, available knowledge, and regulatory compliance are structurally linked with the regulatory framework. The preliminary discussion on liability rules serves the precise purpose of creating a link between regulatory mechanisms and court litigation by addressing issues that are of the essence in both sets of rules: their relationship to risk and its assessment. The intent is to set the scene as regards the attitude of liability rules towards risk in pharmaceutical products, because it is within the sphere of tort law that the thesis examines to what extent it is possible to rely on courts for the purposes of refining the quality of risk assessments, legitimising the system, and enhancing the delivery of safety. As the thesis seeks to argue for a pedagogical role of courts that goes beyond the traditional ones, classically divided between compensation and deterrence, examining the core rules is the necessary preliminary step. The question here is whether or not a substantial margin of manoeuvre exists for courts to intervene and

complement the outcome of regulatory schemes.

The argument moves forward to an analysis of the judiciary's contribution to the availability and quality of scientific data, levels of participation understood in terms of access to justice, and the delivery of safety. The first aspect is data quality. Through the analysis of both specific case law and essential product liability constitutive elements, the thesis considers the extent to which courts can be called upon to bring added value to the regulatory system in terms of quality and accessibility of scientific data for risk assessments. In other words the question is whether through judicial intervention, scientific evidence that gets lost or withheld in the regulatory process can be uncovered and integrated in specific risk assessments, or made generally available for more diverse purposes. The ability to authoritatively impose full disclosure of information enables courts to overcome an impasse with which regulatory authorities are systematically confronted: the necessity of reliance on partial data (which is systemic to an extent, but also very much a product of transnational regulatory processes and practices alluded to above). Beyond its impact on the adjudication of individual claims, this ability can influence the shape of the regulatory system at large. Through focused interventions courts can impact access to information beyond the boundaries of a single case – and arguably all the way to legislative reform. While the oversight thus provided is occasional and necessitates a more diffuse and continuous supplement, the outcome is potentially far reaching.

Related to the issue of partial data is the issue of reliability of that data. What is the level of awareness within the judiciary as regards the flaws of the regulatory framework? What awareness as to the subtleties of flaws relating both to an approval process grounded on limited data in pre-marketing assessments (a limitation aggravated by the increasingly transnational nature of the data relied upon), and to the intrinsic limits of post-marketing measures (which can prove to be slowly reactive rather than effectively proactive)? An analysis of litigation suggests that, whatever the level of judicial awareness, the reality to date has been a generally deferential approach to regulatory findings which typically restrains courts from questioning the origin of emerging safety issues – arguably the regulatory architecture itself – confining the enquiry exclusively to case-specific conduct.

As for the courts' willingness to consider data not disclosed or relied upon in a particular regulatory approval process, the analysis digs into the levels of inclusiveness achievable through judicial oversight. The thesis argument suggests that, if courts are to play a proactive and pedagogical role in enhancing regulatory processes, an activist approach could and should be promoted on the basis of the current legal framework, as the necessary ingredient to challenge the dichotomy between formal and substantial compliance hinted at above. A thorough fact-finding process can pose a legitimate challenge to a regulatory assessment on the ground of failure to achieve desirable safety levels as prescribed by law.

Beyond the scrutiny of data quality, the analysis confronts the issue of access to justice in pharmaceutical cases to question the ability of courts to undertake their complementary function – to act as *surrogates* for participatory democracy as the thesis provocatively suggests. This is an essential step in building the general argument which suggests a balancing 'pedagogical' intervention through 'judicial governance' for a regulatory system very much designed on market-state premises. Naturally, the question is a complex one, and a discussion of access to justice is fundamental to the assessment of whether courts can be effectively reliable agents.

To discuss accessibility in a sustainable way, functional to the general scheme of the work, the focus is on two separate but mutually influential aspects. First, a complex issue linking the themes of data availability and access to justice is that of causation. Proof of causation is without question the toughest burden that product liability imposes on plaintiffs. A discussion of the intricacies of reconstructing the causal links between the use of a pharmaceutical product and allegedly related harms is necessary to show how this essential step constitutes a major hurdle in accessing judicial oversight. The dichotomy between general and specific causation, particularly complex in pharmaceutical products (the effects of which intrinsically vary from patient to patient), calls for significant judicial effort in engaging with a highly technical field.

Beyond the complexity of single cases, accessibility requires the thesis to confront the long-lasting debate opposing individual and collective redress. Whether or not courts can constitute participatory agents depends, at least partially, on this assessment. The hypothesis here is that the answer is more to the positive when mechanisms for collective

redress are in place, because when individual cases are brought to court the obstacle of causation can be simply too burdensome for single parties. While there is arguably potential for courts to complement a regulatory system through questioning the fact of compliance with substantial legal requirements, this complementarity can be fully operational only when the causation obstacle is overcome. As collective mechanisms facilitate the successful defeating of that obstacle, the US seems to remain better equipped than the EU in the promotion of judicial oversight.

The final aspect of the role of the judiciary and litigation in complementing regulatory processes touches upon the complex issue of the adequacy and reliability of litigation outcomes in complex fields such as pharmaceutical safety. The classic arguments against judicial oversight of the outputs of technical regulatory processes are essentially two. First, courts are unprepared to tackle difficult scientific issues, and should therefore defer to the outcome of regulatory assessments (if the possibility of review is to be entertained at all). The second argument is that litigation is an inefficient means of regulatory oversight because of the inherently high transaction costs and prolonged timelines involved. Correlated to both, there is a more general argument that product liability cases do not provide any measurable social benefit, and that a system based on regulatory minimum standards and self-regulatory market incentives is best suited for the governance of product safety at large.

The thesis confronts these arguments in turn, with no ambition to rebut them in a definitive fashion, but rather by suggesting pointers to the adequacy on the one hand and fruitfulness on the other of court cases in the pharmaceutical context. For this purpose, the analysis focuses first on how the alleged technical incompetence of courts can be overcome in practice by their ability to make important value-based judgment calls in the face of uncertainty – with impacts and implications possibly reaching beyond the boundaries of the single case at hand. Secondly, the series of cases considered throughout the thesis underpins the claim that fortuity of risk discovery and delays in swiftly addressing safety issues upon their discovery are structural to the regulatory system. Experience from these cases points to the existence of an identifiable and non-negligible trend where, in the presence of emerging safety issues, the regulatory system takes action *as a consequence* of litigation – either after the case has started or after it has been decided or settled. Administrative actions such as suspension of marketing authorisation or

re-labelling of products have often lagged behind private litigation initiatives. The evident difficulties for regulators in acting upon emerging safety issues make room for the argument that courts can and already are in fact exercising an important surrogate post-marketing surveillance function.

This observation will serve as a bridge to the discussion of the ‘pedagogical role’ of courts that inspires the thesis and its title. The claimed deficiencies of product liability are rebutted with a reflection going beyond an analysis of cost to the substantive role of court decisions. The dismissive argument falls short of addressing the genuine compensatory function of product liability cases, but also of recognising the role of courts in complementing regulatory outputs with decisions on issues ranging from accessibility of relevant knowledge to the interpretation of scientific evidence, not to mention the impetus they provide for regulatory reform.

In sum, the thesis surveys the various threads which lead to a renewed role for courts in tackling safety issues at their origin. The concluding argument for courts to complement regulatory schemes of pharmaceutical safety draws together those threads and re-systematises them to confront the questions and hypothesis raised throughout this introduction and in greater detail in the following chapter I. Can a judicial ‘hard look’ at regulatory processes be beneficial from the perspective of enhancing consumer safety? The answer must be yes. Problematic regulatory features exacerbated by the increasing transnational development of standards and procedures call for renewed in-depth monitoring from a perspective external to the regulatory system’s mechanisms. A ‘pedagogical role’, we argue, for courts.

CHAPTER I²

FACING DIFFERENT TYPES OF *REBUS* IN PHARMACEUTICAL REGULATION

A CRITICAL OVERVIEW OF THE PHARMACEUTICAL SAFETY REGIME

This opening chapter introduces the fundamental issues characterising the pharmaceutical safety regime, which is often referred to subsequently as a ‘system’, and in particular a *closed and self-perpetuating* one.

Two caveats: first, the term ‘system’ as we use it here refers to the complex of ‘soft rules’, ‘hard’ regulations, and laws that play a role in the governance of pharmaceutical product safety. It is used neither in the technical sense of a ‘legal system’³ nor in its sociological meaning.⁴ Secondly, when we refer to the system as *closed* we suggest that it attempts to function in a way impermeable to exogenous influences, whereas the idea of *self-perpetuation* refers to the dynamic and resilient nature of the system, which does not remain static in one specific configuration but develops independently over time, adapting to evolving socio-institutional scenarios.

The chapter starts with a somewhat extreme example to illustrate from the very beginning what is intended by the phrase *closed and self-perpetuating system* and to highlight the questions the thesis attempts to address.

² This chapter is loosely based on a previous work: Rizzi M., “Regulating risks in pharmaceutical law: the need of an optimal interplay between products safety and products liability”, *Opinio Juris in Comparatione*, Vol. 1/2011, Paper No. 2, available at SSRN: <http://ssrn.com/abstract=1857434>.

³ The concept of a legal system refers to the whole of a legal order (a symbolic-normative phenomenon) and legal practices (where the legal order is produced and reproduced: such as law making, adjudication and legal scholarship). The literature here would be overwhelming, but the strongest definition of a legal system is possibly that provided by Hart H.L.A., *The Concept of Law*, Oxford University Press, 2012.

⁴ As elaborated by Luhmann throughout his lifelong work: see for example Luhmann N., *Introduction to Systems Theory*, Wiley, 2012.

1. A tell-tale sign of a structural problem

In the summer of 2009, the WHO officially declared a state of global pandemic⁵ following the outbreak of a new strain of A-N1H1 virus, better known as ‘swine flu’.⁶ The outbreak started in Central America, in the state of Veracruz in Mexico, and spread globally. The ensuing increasing anxiety of the international community led to the prompt adoption of extraordinary measures to avert a potential global health disaster. In particular, massive quantities of A-N1H1 influenza vaccine, subject to ‘fast-track’⁷ approval procedures, were swiftly made available by regulatory agencies. In order to ensure the supply of the vaccine to soothe public opinion, states discharged companies from tort liability in case of damages,⁸ and assumed full responsibility for the risks created by the widespread distribution of a not-thoroughly-tested vaccine in their communities.

The following winter (2009-2010), the pandemic gradually started to diminish, and by August 2010, the Director-General of the WHO, Dr Margaret Chan, declared the end of the A-N1H1 pandemic.⁹ Looking at the numbers, the pandemic could have been much worse, or maybe should have been much worse, in light of the level of alert and subsequent social anxiety. In the space of one year, the A-N1H1 virus had killed approximately 18,000 people globally.¹⁰ That is about four per cent of the 250,000 to 500,000 annual deaths caused by ‘regular’ influenza.¹¹ Many critical voices raised the objection that the WHO had overstated the actual risk and diffused “fear and confusion” instead of “immediate information”.¹² However, WHO Director-General Chan had

⁵ See the statement to the press by the WHO Director-General, Dr. Margaret Chan, at http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/index.html.

⁶ An interesting reconstruction questioning the constitutional implications of the case for EU health policy is de Ruijter A., “The Constitutional Implications of European Public Health Policy”, *ACELG Working Paper Series*, 2010/05.

⁷ See chapter II on the ‘fast-track’ approval procedures.

⁸ The contracts between producers and Member States in the EU for the sale and distribution of A-N1H1 vaccine are characterised, Europe-wide, by the explicit provision of liability exemption clauses. See for example the contract between Novartis and the Italian government, available at <http://www.altreconomia.it/allegati/contenuti/phpXkxW0S2095.pdf>.

⁹ See http://www.who.int/mediacentre/news/statements/2010/h1n1_vpc_20100810/en/index.html.

¹⁰ By late July 2010, the WHO was still considering the virus a pandemic, on the basis of the same statistics: see the relevant documents available at <http://www.who.int/csr/disease/swineflu/en/>.

¹¹ WHO fact sheet communication N° 211, April 2009, *ibidem*.

¹² Lynn J., “WHO to Review its Handling of N1H1 Flu Pandemic”, Reuters, January 10, 2010, available at <http://www.reuters.com/article/2010/01/12/us-flu-who-idUSTRE5BL2ZT20100112>; see also the New York Times’ ‘Health Guide’ on H1N1 Influenza, available at <http://www.nytimes.com/health/guides/disease/h1n1-swine-influenza/overview.html>.

explicitly underlined that the number of deaths worldwide was comparatively small, adding that “we do not expect to see a sudden and dramatic jump in the number of severe or fatal infections”.¹³ Questions were thus raised about the necessity of states investing billions in the purchase of enormous quantities of a vaccine, the safety and efficacy of which were “far from being certain”.¹⁴ Then, quietly and smoothly, this story slowed down and disappeared.

What happened here? The answer raises fundamental questions regarding the essence of the relationship between risk and law, as well as the nature and role of law in a global world. The ‘swine flu’ pandemic is a paradigmatic example of a panic/non-routine situation that challenges an entire system of laws and regulations, highlighting the shortcomings and weaknesses of the system itself. What is striking about the story of the A-N1H1 vaccine is that the pharmaceutical ‘system’ (the complex interaction of international/transnational organisations, regulatory authorities, and pharmaceutical industries we referred to as *closed*) created, reacted to, and then erased a crisis in an entirely ‘endogenous’ way. Sovereign states and their communities, albeit being primarily affected by the results of the system’s decisions, had little role in the governance of the issue, assuming instead a rather passive stance in accepting the system’s outputs.¹⁵

A caveat is necessary. The A-N1H1 pandemic was, allegedly, an emergency situation¹⁶ for which special procedures were in place to guarantee a rapid response to potentially catastrophic consequences. The focus of this work is not specifically on emergency situations nor is it on the A-N1H1 vaccine. This atypical example is raised as an opportunity to illuminate certain features of the system within which it occurred, or which *allowed* it to occur. Prominent French sociologist Francis Chateauraynaud describes how

¹³ See WHO, “The international response to the influenza pandemic: WHO responds to the critics” at http://www.who.int/csr/disease/swineflu/notes/briefing_20100610/en/, where it is argued that “[i]n every assessment of the pandemic, WHO consistently reminded the public that the overwhelming majority of patients experienced mild symptoms and made a rapid and full recovery, even without medical treatment”.

¹⁴ As explicitly emerged in an event promoted by the British Institute of International and Comparative Law in the wake of the ‘swine flu’ crisis, *Regulatory Standards & Liability: Developing the Appropriate Assessment Model for Medicines*, September 2010.

¹⁵ The aforementioned explicit provision of liability exemption clauses in the sale contracts of A-N1H1 vaccines is a good example, but it is possible more generally to identify a tendency of states to be rule-takers with no real power in the rule-making process, as shall be examined in the following sections and chapters.

¹⁶ That is, a response to the WHO technically declaring a state of pandemic. How real the emergency and how serious the threat is an entirely different story.

referring to an extreme situation has a strong pedagogical value for explaining the routine, as the extreme exacerbates the problematic issues that are inherent to the society or group under scrutiny under ‘normal’ or, shall we say, non-emergency or routine conditions.¹⁷ In the present case, what emerges from the A-N1H1 story is the appearance of a *self-perpetuating*¹⁸ and *closed* system of decision-making in the field of pharmaceutical products that operates with substantial independence from state oversight and more generally from forms of democratic control that are traditionally linked to rule-making powers. The questions to be addressed are therefore: what does this mean exactly? Why is it so? And why is this fundamentally problematic?

2. A twofold discourse: law and science, law and transnationalisation

The questions are complex and constitute the ‘causal quest’ of the thesis. A satisfying analysis requires an accurate description, or cartography,¹⁹ first of the institutions and actors of the system and then of the dynamics within the system. To engage in the suggested description it is necessary to consider the significant phenomena that will be encountered in this process. We can identify two principal candidates.

The first is the delegation of decision-/rule-making power from public governments to scientific expert bodies. Because of the extremely high level of technicality characterising increasing numbers of social sectors, in the second half of the 20th century a trend began towards progressively higher reliance on the assessments of bodies and committees with great technical expertise (and thus an aura of neutrality)²⁰ in

¹⁷ Chateauraynaud F., Torny D., *Les Sombres précurseurs: Une Sociologie pragmatique de l’alerte et du risque*, Paris, EHESS, 1999; see also Chateauraynaud F. “La Sociologie pragmatique à l’épreuve des risques – Exercice de crise sur le dossier nucléaire”, *Politix*, n°44, 1998, pp. 76-108: the argument being that the weaknesses of physiological societal dynamics are better explained by pathological outbreaks.

¹⁸ Systems theorists would use the term *autopoietic*: see the fundamental text by Teubner G. (ed.), *Autopoietic Law: A New Approach to Law and Society*, Walter De Gruyter, Berlin, 1988; and Michailakis D., “Law as an Autopoietic System”, *Acta Sociologica* 38, 1995. The term is avoided in this thesis as this is not a systems theory analysis.

¹⁹ Santos B.S., “Law: A Map of Misreading. Toward a Postmodern Conception of Law”, *Journal of Law and Society*, Vol. 14, No. 3, 1987, pp. 279-302.

²⁰ See among others Lentsch J., Veingart P. (eds), *The Politics of Scientific Advice: Institutional Design for Quality Assurance*, Cambridge University Press, 2011; Shapin S., *The Scientific Life – A Moral History of a Late Moral Vocation*, The University of Chicago Press, 2008; and Topf R., “Science, Public Policy, and the Authoritativeness of the Governmental Process”, in Barker A. and Peters G., *Expert Advice*, University of Pittsburgh Press, 1993.

specific fields. At first this reliance created a complex situation with a progressive detachment between scientific sector-specific knowledge on the one hand, and the actual wielders of policy-making power on the other. But the growing gap in the expertise required to make learned decisions on technical issues led rapidly to a *de facto* delegation of policy-making power to the expert bodies. The result was the emergence of highly qualified bodies in specific technical fields, able to understand from a scientific point of view the risks and stakes involved in each assessment decision, but also empowered to make policy decisions for which they arguably lacked the necessary legitimacy on the one hand, and competence on the other.²¹ The birth and growth of agencies such as the FDA in the US and the EMA in the EU are perfect examples of such a trend.²² There are several risks inherent in the delegation of decision- and rule-making power to agencies, risks that are to a certain extent unavoidable but that call for measures of oversight from the delegator, i.e. the state. For instance, agencies may lack the necessary strength to resist lobbying pressures or may adopt biased attitudes, triggering typical situations of ‘regulatory capture’.²³ The delegation process has nonetheless ensued, and is thoroughly and clearly explained by Sheila Jasanoff in a book effectively titled *The Fifth Branch*.²⁴ Through a series of case studies including the most relevant US federal agencies,²⁵ the book shows how advisory committees and expert consultative bodies, thanks to effectively inescapable reliance on their specific competences, have gained, since the middle of the 20th century, increasing shares of real decision-making power, to the extent that they now constitute the ‘fifth branch’ of the American government. The checks and balances

²¹ Within the florid literature on the legitimacy and competence of independent committees in decision-making, see among others Blom-Hansen J., *The EU Comitology System in Theory and Practice: Keeping an Eye on the Commission?*, Palgrave, 2011; Dammers W.F., *Comitology in the Decision-Making Process of the European Union*, Wolf Legal Publishers, 2008; Jorge C., Ladeur K.-H., Vos E. (eds), *Integrating Scientific Expertise into Regulatory Decision-Making: National Traditions and European Innovations*, Baden-Baden, 1997; and Jasanoff S., *The Fifth Branch - science advisers as policy makers*, Harvard University Press paperback edition, 1994.

²² See the discussion in chapter II.

²³ On the topic of ‘capture’ see among others Ogas A.I., *Regulation: Legal Form and Economic Theory*, Hart Publishing, 2004, p. 57: “the ineffectiveness of regulatory agencies in meeting the public interest goals assigned to them could most plausibly be explained by assuming that they had been subverted by pressure, influence, and ‘bribery’ to protect the interests of those who were the subjects of the regulation”; see also the more recent Carpenter D., Moss D.A., *Preventing Regulatory Capture – Special Interest Influence and How to Limit it*, Cambridge University Press, 2013.

²⁴ Jasanoff S., *The Fifth Branch*; see also Jasanoff S., *Science at the Bar: law, science and technology in America*, Harvard University Press paperback edition, 1997.

²⁵ The Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), the Food and Drug Administration (FDA), and the Clean Air Scientific Advisory Committee (CASAC).

between the sectorial experts who understand the scientific risks, and the policy-makers who should manage the needs and fears of society, are weighted, it appears, in favour of the former.²⁶

The second significant phenomenon characterising the pharmaceutical regulatory system is that already referred to as transnationalisation, specifically of the regulations and standards regarding the procedures propaedeutic to the marketing approval of a new product. The globalisation process is profoundly modifying the issues confronting lawmakers,²⁷ but conventional legal discourse does not seem able to keep pace with the speed of this transformation. As a matter of fact, on the one hand states are losing (or have already lost) their traditional centrality in the international discourse, as well as their role of necessary and non-fungible rule-makers;²⁸ while on the other hand we are witnessing an irresistible and continuous tendency towards fragmentation of the social space in specific sectors, which are gaining independence *vis à vis* each other, and *vis à vis* the states.²⁹ In other words, the social space to be regulated has crossed the borders of the political space of the nation state, significantly weakening the capacity of national law to respond to regulatory needs.³⁰ States and their laws are giving way to transnational social sectors (or, arguably, ‘systems’ as we have described them), one of which, we contend, is the pharmaceutical market. Within the vast legal scholarship addressing the ‘transnational law’ phenomenon, our system of interest could fit the definition of what Paul Schiff Berman describes as a *hybrid legal space*:³¹ a social space in which a plurality of legal orders

²⁶ Jasanoff S., *The Fifth Branch*, pp. 216-222.

²⁷ This is not the place for a review of the literature in the field of post-national law; readers are referred to the comprehensive summarising efforts of Kaarlo Tuori in “Towards a Theory of Transnational Law” (unpublished paper, 26 August 2010); and more recently Maduro M., Tuori K., Sankari S., *Transnational Law – Rethinking European Law and Legal Thinking*, Cambridge University Press, 2014.

²⁸ We suggested the existence of this phenomenon above while discussing the delegation of decision-making powers to independent agencies. So the issue is really two-fold: states lose their rule-making powers internally via delegation, and transnationally as they become ‘rule-takers’. The shift from the state as a rule-maker to the state as a rule-taker is explained by Cafaggi F., “New Foundations of Transnational Private Regulation”, 38 *Journal of Law and Society* 1, 2011, pp. 20-49. In that context the shift is described in the frame of transnational private regulation (TPR), whereas the context of the present study is rather one of transnational regulatory networks (TRN), but conceptually the idea translates.

²⁹ On the validity of Niklas Luhmann's speculative hypothesis that “global law would experience a radical fragmentation, not along territorial, but along social sectorial lines” see Teubner G., Fisher-Lescano A., “Regime Collisions: The Vain Search for Legal Unity in the Fragmentation of Global Law”, 25 *Michigan Journal of International Law*, p. 999.

³⁰ Tuori K., “Towards a Theory of Transnational Law”, p. 4.

³¹ Berman P.S., “Global Legal Pluralism”, 80 *California Law Review*, 2008, pp. 1155-1237.

and systems of norms coexist and interact. Complementary to this approach is the idea of *interlegality* as developed by Boaventura de Sousa Santos. *Interlegality* is characterised by “different legal spaces superimposed, interpenetrated and mixed in our minds, as much as in our actions”, and “porous legality” where “multiple networks of legal orders” are interlinked.³² This idea seems to be perfectly applicable to the pharmaceutical regulatory framework, where regional and national public regulations, transnational soft law, transnational regulatory networks, national and regional agencies, mechanisms of enforcement, and private individual or collective redress mechanisms coexist in the same social space, giving birth to a fascinating entanglement. An entanglement that seems yet to be fully grasped, given that pharmaceutical regulation is still generally studied and understood as a national or regional phenomenon.³³

To use the terminology adopted by Saskia Sassen, what is needed is an analysis that sheds light on the complex *assemblages*³⁴ of normative levels, from the transnational network to the local implementation of regulatory practices. This clarification is necessary to move forward into the implications of the *relocation* of the state³⁵ from *ex-ante* rule maker to *ex-post* rule-receiver both at a descriptive level (through the observation of current rule-making and enforcement mechanisms where states have relocated the *locus auctoritatis*) and at a normative one (with a discussion of the actual and potential role of national courts in re-creating a form of state authority through post-marketing scrutiny).

The transnational space is difficult to define, but confronting this difficulty is necessary to avoid ‘tunnel views’ limiting it to the “sphere of action of international organisations, the extra-territorial intervention of the states, or the transnational activities of private entities”.³⁶ Avoiding such tunnel views is key to moving beyond the current typical focus on national/regional entities, to achieve a realistic understanding of the regulatory mechanisms of the pharmaceutical market.

³² Santos B.S., *Toward a New Legal Common Sense*, 2nd ed., Butterworths, 2002.

³³ As will be discussed in chapters II, III and IV.

³⁴ Sassen S., *Territory Authority and Rights – From Medieval to Global Assemblages*, Princeton University Press, 2006.

³⁵ Sassen S., “Immigration Policy in a Global Economy”, 17 *SAIS Review* 2, 1997, pp. 1-19.

³⁶ Duval A., “Lex Sportiva: A Playground for Transnational Law”, 19 *European Law Journal* 6, 2014, p. 823.

3. Transnationalising pharma – is there a ‘risk’ in the understanding of risk?

The study began with an example supporting the claim that the pharmaceutical sector functions as a self-perpetuating system of regulation essentially closed to exogenous inputs. The last paragraph raised the issue of transnationalisation. The question to be addressed now is: what is the transnational element in pharmaceutical law? Pharmaceutical innovation tends to be handled by a relatively restricted group of multinational industries,³⁷ and new products are marketed after they undergo clinical trials in different countries obeying different rules and standards – and those new products are frequently the result of combining active ingredients discovered and produced in different places.³⁸ Our initial example, the A-N1H1 vaccine, is useful to illustrate the issue. The vaccine is a modified version of another one, originally developed for the prevention of a previous strain of influenza A (H5N1), commonly referred to as ‘bird flu’. When the A-N1H1 virus started to spread in the summer of 2009, given the high level of potential threat to public health, the FDA and the EMA approved for fast-track testing³⁹ the use of an experimental (and not yet marketed) treatment developed in South East Asia⁴⁰ for the prevention of ‘bird flu’. The final product, the A-N1H1 vaccine, was the result of cooperation between the

³⁷ O'Donnell J.T., *Drug injury – liability, analysis and prevention*, Lawyers & Judges Publishing Company, Inc., 2001, p. 121 ff; the total amount of sales has now increased also in export trade. In 2006 sales were estimated at 29.4 billion Euros, 16.2 billion Euros of which resulted from export trade. Worldwide the total amount of sales was 643 billion US dollars in 2006: see Purnhagen K., *The Challenge of Globalization in Pharmaceutical Law*, p. 623; Spitz J., Wickham M., “Pharmaceutical High Profits: the Value of R&D, or Oligopolistics Rents?”, *American Journal of Economics and Sociology* 71, 2012.

³⁸ This is by now an accepted fact that will be discussed extensively in chapters II and III, see for example Communication of the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, *Safe Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector*, Brussels, 10 December 2008; a trend confirmed as steadily increasing in the succeeding EMA publication, “Clinical Trials Submitted in Marketing Authorization Applications to EMA: Overview of Patients recruitment and the Geographical Location of Investigator Sites”, Doc. Ref. EMA/INS/GCP/676319/2012, 11 December 2013, available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf.

³⁹ The so-called ‘mock procedure’, which is an *ad hoc* speed-approval, aimed at facing serious and immediate threats to public health, in which testing is basically spread through a minimal pre-market phase and a critical post-marketing phase. In other words, the general public becomes the subject of a mass clinical trial. See records of the fast-track emergency approvals, available at www.fda.gov/biologicsbloodvaccines/safetyavailability/vaccinesafety/ucm161448.htm for the FDA and www.ema.eu/docs/en_GB/document_library/Report/2010/01/WC500044933.pdf for the EMA.

⁴⁰ Specifically in Thailand, where the experimental vaccine had been approved for phase I clinical trial only in 2012: see US Department of Health & Human Services press release of June 7, 2012, available at www.phe.gov/Preparedness/news/Pages/International-flu-vaccine-120607.aspx.

US and EU pharmaceutical regulatory agencies, based on the provisional results of a procedure conducted in a third country.⁴¹

Again, A-N1H1 was an emergency response. However it exposes an issue that is of crucial importance in understanding the contemporary criticalities of the pharmaceutical market. The market is global, and so are its actors, the innovators and producers. Thus the problem is *quid?* when a product undergoes a procedure that is de-localised or multi-localised, but the marketing authorisation procedures are structured nationally or regionally. Two competing considerations arise from this question. On the one hand the pharmaceutical industry, together with the EMA and the FDA, has been strongly pushing for mechanisms avoiding repetition of procedural steps in order to guarantee “a prompt and efficient availability of much needed new treatments”.⁴² On the other hand, the necessity of ensuring high levels of oversight from a safety and efficacy perspective is clear. Drug testing is intimately linked to conceptions and understandings of key notions, such as the one of ‘risk’, known to be highly variable across cultures.⁴³ This is not a merely abstract point as it has direct consequences on “where and how one draws the line between still acceptable, and no longer acceptable exposures”.⁴⁴ The attitude of societies towards *manufactured risks*,⁴⁵ for example, impacts directly on the modes of conducting clinical trials.⁴⁶ Further, structures and modes of interaction between

⁴¹ A thorough reconstruction of the history of the A-N1H1 vaccine can be found in the very detailed analysis of two prominent scholars (a pathologist and a microbiologist), Bologna M., Lepidi A., *Pandemie: virologia, patologia e prevenzione dell'influenza*, Bollati Boringhieri, 2010.

⁴² As repeatedly stressed by both the EU Commission and the US FDA in policy documents. The relevant quote is taken from the Communication of the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, *Safe Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector*, Brussels, 10/12/2008.

⁴³ There are several studies on how cultural diversity influences risk perception: see for example the essential book Hofstede G., *Culture's Consequences: comparing values, behaviours, institutions, and organizations across nations*, 2nd ed., SAGE, 2001. An analysis of how risk perception is first of all an individual, and subsequently a social process can be found in Luhmann N., *Risk: A Sociological Theory*, Walter de Gruyter, 1993.

⁴⁴ Beck U., *Risk Society – Towards a New Modernity*, Sage Publications, 1992, p. 29.

⁴⁵ Giddens A., “Risk and Responsibility”, 62 *Modern Law Review* 1, 1999, p. 4: “Manufactured risk is risk created by the very progression of human development, especially by the progression of science and technology. Manufactured risk refers to new risk environment for which history provides us with very little previous experience.” Manufactured risk is contrasted with *external risks*, which are related “to events that may strike individuals unexpectedly from the outside, but that happen regularly enough and often enough” to be broadly predictable.

⁴⁶ A classic example of an EU/US clash can be found in the way clinical trials are conducted in Phase III of pre-marketing assessments, where the FDA is more stringent in requiring tests against placebo whereas the EMA is more inclined towards tests against available alternative treatments. This issue is related to different interpretations of the Declaration of Helsinki of 2008 on biomedical research

physicians, regulatory agencies, drug companies, and consumers, which are just as variable, contribute to create something that has been aptly referred to as a nation's 'therapeutic culture'.⁴⁷ The recognition and adoption of steps in procedures that are multi-locally conducted must therefore confront these issues, as they are inherently liable to result in differences in the substance and practice of specific local regulations affecting safety assessments. Local regulatory systems (the only real 'hard law' in play), with local regulatory agencies at their head, cannot be expected to address in a satisfying way the issue of multi-local production and testing of new products. The safety of medicine consumers needs to be understood rather as a globalised mass phenomenon, and addressed accordingly.

A major initiative in this respect was launched in 1990 by the ICH, which as described in the Introduction is a permanent forum representing drug regulatory authorities of the US, EU, and Japan and regional industry representatives. ICH seeks to harmonise drug testing through protocols and voluntary agreements⁴⁸ in order to improve the quality of transnational safety requirements by finding an appropriate balance between competing regulatory styles. The thesis will explore the shortcomings of ICH guidelines in addressing substantive issues in chapter III, and question the legitimacy and accountability of ICH as an institution in chapter IV.

In a snapshot, as regards legitimacy, ICH presents two sets of issues. First, the network is constituted by a limited number of stakeholders – regulators and industry – leaving other essential categories (such as physicians and patients) out of the picture. Secondly, countries such as Brazil, India, and China, originally excluded from the ICH forum, are now emerging as major players in the field of pharmaceuticals, and already host

on human subjects: see the discussion in chapter III.

⁴⁷ The term is used by Dr. A. Daemrich in *Pharmacopolitics – Drug Regulation in the United States and Germany*, The University of North Carolina Press, 2004, p. 243 ff.

⁴⁸ The process of harmonisation undertaken by the ICH will be further described in the following chapters II and IV: suffice to say that the procedure requires the adoption of a Concept Paper by the Steering Committee. The nature of the guidelines issued through such procedure is controversial, see *infra*, and for a discussion Purnhagen K., "The Challenge of Globalization in Pharmaceutical Law: Is an International Approval System Modelled after the European System Worth Considering?", 63 *Food and Drug Law Journal*, 3, 2008, pp. 623-645; and Berman A., "The Role of Domestic Administrative Law in the Accountability of IN-LAW: The Case of the ICH" in Pauwelyn J., Wessel R., Wouters J. (eds.), *Informal International Lawmaking: Mapping the Action and Testing Concepts of Accountability and Effectiveness*, Oxford University Press, 2012.

significant portions of the research and testing process for new drugs.⁴⁹ In order to involve emerging markets, ICH members have created an advisory body, the Global Cooperation Group, which seeks to promote broader international harmonisation.⁵⁰

On the effectiveness side, the concerns are again twofold. On the one hand there is the typical problem of transnational regulatory networks (TRN)⁵¹ where participants are often tied to their authority (or constituency in the case of business representatives) of origin in a way that generally outweighs their loyalty to global interests.⁵² On the other hand, the presence of divergent ‘therapeutic cultures’ creates a series of conflicts based on different understandings of key notions that lie at the very basis of safety regulation (such as, again, the notion of risk, the aversion to or embracing of it).⁵³ These observations, as they will be developed in the following chapters, suggest that there is room to doubt the real strength and autonomy of a *transnational legal culture*⁵⁴ in the field. However, despite these briefly sketched concerns, in everyday practice the discovery, testing, and approval of a new pharmaceutical is in fact a widespread transnational phenomenon.⁵⁵ From this factual observation we propose two hypotheses.

The first hypothesis posits the concrete possibility that the increasing number of bodies involved across the world in the approval process of a new product, combined with the incomplete international harmonisation of the relevant regulatory rules and standards, generates a non-negligible level of uncertainty as regards the scientific knowledge

⁴⁹ The data on clinical test outsourcing are discussed in chapter III.

⁵⁰ The Global Cooperation Group (GCG) was conceived at first as a subcommittee of the ICH Steering Committee in 1999. This was the first response to an increasing interest in ICH Guidelines beyond the three original ICH regions. In the early 2000s, “recognising the need to engage actively with other harmonisation initiatives, representatives from five Regional Harmonisation Initiatives (RHIs) were invited to participate in GCG discussions, namely, APEC, ASEAN, GCC, PANDRH and SADC. A further expansion of the GCG was agreed in 2007 and regulators were invited from countries where major production and clinical research is done (Australia, Brazil, China, Chinese Taipei, India, Republic of Korea, Russia and Singapore)”: see the ICH Organisation as set out at <http://www.ich.org/about/organisation-of-ich/coopgroup.html>.

⁵¹ A critical analysis of transnational regulatory networks can be found in Verdier P.H., “Transnational Regulatory Networks and their Limits”, 34 *Yale Journal of International Law* 113, 2009.

⁵² Verdier P.H., “Transnational Regulatory Networks and their Limits”, p. 162.; *contra* see Slaughter A.M., *A New World Order*, Princeton University Press, 2004, pp. 131-162; see also Fenwick M., Van Uytsel S., Wróblek S. (eds), *Networked Governance, Transnational Business and the Law*, Springer, 2014.

⁵³ This will be further discussed in chapter III.

⁵⁴ The idea is suggested by Tuori K., “Towards a Theory of Transnational Law”. A transnational legal culture emerges in a field where rule-makers cooperate at a supranational level. The idea is that through time, they develop a common legal culture autonomous from their original one – they start to ‘think’ supranationally and in the interest of the supranational endeavour.

⁵⁵ See the in-depth analysis in chapter III.

employed in the assessment process. Chapter III will discuss this prospect.

The second hypothesis is that the current structure of transnational rule-making is struggling (or consciously failing) to achieve its self-attributed mandate of harmonising technical standards. The ICH is however taking strong value-based decisions that surpass that mandate, upholding trade considerations as a primary goal, with safety and efficacy as subsidiary ones. Chapter IV will explore the cases of Good Clinical Practice (GCP) and Statistical Principles for Clinical Trials (SPCT) guidelines to support this claim. Whereas it is represented and perceived as a network of sectorial experts addressing highly technical issues (and producing highly technical outputs – difficult reading for non-experts),⁵⁶ the ICH is really a public-private platform where core choices on levels of exposure are negotiated. This, we posit, is a fundamental regulatory choice⁵⁷ that should be appreciated in its full extent when analysing pharmaceutical regulation – a transnational and no longer primarily national/regional phenomenon.

It now becomes necessary to clarify the consumer safety perspective that informs the analysis throughout this study.

4. The consumer safety perspective – two sides of a coin

Consumers are directly affected by the decisions deriving from safety assessments made by scientific experts through regulatory procedures. This study therefore takes the perspective of the level of safety that is delivered by the system. The increasingly globalised nature of the pharmaceutical market invites critical analysis of the shape and functioning of the existing national and regional legal frameworks that are meant to ensure safety. Until now the chapter's focus was on the procedures that lead to the marketing of a new product. However, taking the perspective of consumer safety implies a subsequent focus on 'the other side of the coin': the remedies available in case of damage caused by a product. The extent to which consumers are empowered to react to threats or actual

⁵⁶ For a compelling case in favour of technocratic risk regulation and management see Sunstein C., *Risk and Reason*, Cambridge University Press, 2004.

⁵⁷ On the theory of regulatory choices see Adler M.D., "Regulatory Theory", in Patterson D. (ed.), *A Companion to Philosophy of Law and Legal Theory*, Wiley-Blackwell, 2010, pp. 590-606.

damage forms an integral part of the system meant to ensure their safety.⁵⁸

If consumer safety is a two-sided coin, the two main bodies of law to be considered here are safety regulation and product liability. As for the former, we have already suggested, and we shall see below in more detail,⁵⁹ that the transnationalisation of procedures renders national regulatory differences problematic in terms of consumer protection. As for the issue of remedies for harm, pharmaceutical product liability is a composite field, with reactions as dependent upon local history and culture as upon divergent understandings of risk.⁶⁰ However, unlike regulation, product liability is still predominantly nation-based. The thesis therefore attempts to analyse how reactions in that field promote the protection of consumers from potential damage caused by decisions that are based on transnational as much as domestic rules – as those reactions have the potential, we posit, to unlock the closed regulatory system.

In this perspective, a particularly interesting issue for this study is the federal preemption of state tort law, a doctrine first articulated in drug litigation in the US in 2006. More specifically, in the preamble to its January 2006 prescription drug labelling rule, the FDA asserted that “FDA approval of labelling under the act . . . pre-empts conflicting or contrary State law”.⁶¹ This approach raised several safety concerns in light of the inherent level of scientific uncertainty that characterises a new pharmaceutical,⁶² *a fortiori* in situations in which marketing approval follows a transnational and imperfectly harmonised procedure. Preemption of tort law weakens protection of consumer safety, which is arguably better served by an approach grounded on the theory of ‘functional

⁵⁸ On the role of tort law in contributing to consumer safety, see generally Viscusi W.K. (ed.), *Regulation Through Litigation*, AEI Brookings Joint Center for Regulatory Studies, 2002; Jasanoff S., *Science at the Bar*; and on the idea of pharmaceutical product safety as a sum of drug regulation and product liability see Rizzi M., “Regulating risks in pharmaceutical law”; for recent European trends towards a US-shaped adversarial legalism see Kelemen R.D., *Eurolegalism*, Harvard University Press, 2011.

⁵⁹ See chapter II; for detailed examples, an interesting overview of differences between the EMA and the FDA can be found in <http://biopharminternational.findpharma.com/biopharm/Article/Navigating-Differences-Between-FDA-and-EMEA-for-Re/ArticleStandard/Article/detail/371018>.

⁶⁰ For a discussion on the impact of cultural biases on tort law rules, see Van Dam C., “Who is Afraid of Cultural Diversity? Cultural Diversity, European Co-operation, and European Tort Law”, 20 *King’s Law Journal* 281-308, 2009.

⁶¹ Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006) (effective June 30, 2006) (21 C.F.R. Pts. 201, 314, 601); for a comment see Sharkey C.M., “Preemption by Preamble: Federal Agencies and the Federalization of Tort Law”, *De Paul Law Review*, 56, 2007; and the discussion in chapter VI.

⁶² On the unavoidable level of scientific uncertainty, and thus on the unavoidable level of risk that is inherent in any pharmaceutical product, see in chapter VI the discussion regarding *comments j* and *k* to the *Restatement (Second) on Torts*.

complementarity⁶³ of regulation and liability. This critical issue has been at the centre of both a judicial and a doctrinal debate in the US, where tort law has historically played a major regulatory role, balancing through litigation the numerous shortcomings of regulation.⁶⁴ Albeit abandoned after only three years,⁶⁵ the preemption doctrine represents a significant attempt to make the *closed* system fully impermeable to exogenous forms of control. Contrary to the US, in the EU product liability is a relatively minor field of litigation – although the aggregate figures have been on a slow but steady rise over the past twenty-five years. Consumers are generally protected by other private or public legal tools, namely insurance or social security systems,⁶⁶ which significantly reduce incentives to litigate in case of damage.⁶⁷ The limitations of these mechanisms in ensuring more than simple compensation represent a problematic aspect of the European scenario. It is arguable that parallel systems of recovery in case of damage (coupled with more restrictive access to litigation than in the US – where collective redress mechanisms are far more developed) create a form of indirect preemption of judicial control (locking down, or *closing*, the system again, shielding it from external forms of oversight).

5. The structure and methodology for a cartography of the system – Challenges and comparative choices

Finding a satisfactory methodological approach for this study has been a complex task and the final result is open to potential criticism. This section sets out the method as originally conceived and the adjustments that were necessary to overcome the obstacles encountered along the way. We accept here the idea proposed by Aulis Aarnio that a scholarly study of the law is necessarily aimed at producing knowledge of legal norms and

⁶³ This claim will be further explained in the last section of this chapter. On the doctrine of complementarity see Cafaggi F., *Institutional Framework of European Private Law*, Oxford University Press, 2006, p. 191 ff. The theory of functional complementarity a) on a positive level shows the reciprocal influences of the two techniques, and b) on a normative level calls for a high degree of coordination.

⁶⁴ See for a comprehensive discussion Viscusi W.K., *Regulation Through Litigation*, and for Europe Kelemen R.D., *Eurolegalism*.

⁶⁵ Following the US Supreme Court case decided in March 2009, *Wyeth v. Levine*, 129 S. Ct. 1187, 2009.

⁶⁶ As thoroughly explained by Reimann M., “Liability for defective products at the beginning of the twenty-first century: emergence of a worldwide standard?”, *American Journal of Comparative Law*, 2003.

⁶⁷ See for example Hodges C., “Current Discussions on Consumer Redress: Collective Redress and ADR”, Academy of European Law – Annual Conference on European Consumer Law, 2011.

systematising those norms to provide society with an enhanced understanding of a determined (and problematic) legal order.⁶⁸ Perfect scientific criteria of controllability are hardly applicable to the law⁶⁹ – the notion of *truth* as accepted in natural sciences is of little use in the study of legal phenomena, where the highest achievement can only be a ‘softer version’ of the truth in the form of “well-reasoned certainty”.⁷⁰ It is rather from the notion of *coherence* that a scholarly legal study draws its strength. It follows that legal methodology is by nature “not inductive or deductive but rational *discursive*. The method is legal argumentation, which produces a coherent network of reasons to produce recommendations”.⁷¹ The argument here is built by confronting the rules and institutions governing pharmaceutical regulation (pre- and post-marketing) with the reality of the phenomenon as observed in practice. It necessarily follows that the bulk of the study is descriptive. In order to construct the argument, the thesis is divided into two major parts. The first and lengthier part looks at the regulatory side of pharmaceutical safety – its institutional design, the substantial and procedural issues it faces in the transnational setting, its ability to deliver and ensure safety and efficacy. This will allow us to identify the problems in their concrete dimension. The second part digs into the ability of the judiciary to complement and monitor regulatory actions.

We have already identified the criticalities arising as a consequence of the transnational dimension coupled with what we call ‘expertise’s capture of regulatory power’. The first step of the proposed analysis is therefore to produce a descriptive account of the principal institutional agents of the transnational pharmaceutical scenario: the US FDA, the European EMA, and the ICH. The reasons for this choice are simple. The US and the EU are the two major pharmaceutical markets, in which roughly 80% of the worldwide product is marketed and consumed.⁷² Given the close cooperation that exists between the two as regards marketing approval procedures,⁷³ a reconstruction of

⁶⁸ Aarnio A., *Essays on the Doctrinal Study of the Law*, Springer, 2011, Chapter IV “Lawyer’s Dilemma”.

⁶⁹ *Ibidem*.

⁷⁰ *Ibidem*, p. 28.

⁷¹ *Ibidem*.

⁷² These statistics are widely acknowledged by a number of authors, confirmed by the WHO in “The World Medicines Situation 2011 – Pharmaceutical Consumption”, available at <http://apps.who.int/medicinedocs/documents/s20035en/s20035en.pdf>, in 2011, and not subject to significant variation since.

⁷³ There is an intense exchange of data and coordinated testing for marketing approval between the two agencies. This close cooperation has been reinforced as of 2009 by the appointment of Dr Janice Soreth as the FDA liaison officer to the EMA, and as of 2012 by the appointment of Dr Sabine

how these institutions were born, and how they actually work, is essential to understanding the complexity of their relationship. At the time this thesis is being written, the US and the EU are in the process of negotiating an extensive Transatlantic Trade and Investment Partnership (TTIP) which will impact sectorial regulatory frameworks, including pharmaceuticals.⁷⁴ Information on the structure and content of the TTIP is strictly confidential and difficult to access.⁷⁵ However, what emerges to date is that the negotiation is moving towards the inclusion of “application of good regulatory practices (e.g. consultation, transparency, impact assessment, etc.) into a trade agreement, without however substantially altering the parties’ respective ways of making legislation or rules”,⁷⁶ enabling substantial margins for regulatory mutual recognition and compatibility mechanisms. Because of the prospective nature of the TTIP as a “living agreement”, obligations can be added without reopening the initial treaty.⁷⁷ Alberto Alemanno in particular has observed that in the hypothetical in which regulators were to find “areas of convergence”, they would be able to commit themselves and legally bind their authority of origin. This is because agreements of this sort would be added to the partnership via sectoral annexes. In describing the TTIP functioning Alemanno observes that:⁷⁸

its cooperation mechanism [...] nudges the regulators away from the previously agreed regulatory standards [...] while an agreement reached within a regulatory dialogue [...] does not formally modify the domestic regulatory requirement [...] it implies a departure from it in relation to the imported products or services. This may prompt fundamental accountability problems as the operation of TTIP may result in regulatory processes that gradually appear detached from the previously agreed policy choice and therefore the policy preferences of the

Haubenreisser as the EMA liaison officer to the FDA.

⁷⁴ See EU Commission, “Note for the attention of the Trade Policy Committee - Annex III Initial Position Paper on Pharmaceuticals”, 20 June 2013, available at <http://www.iatp.org/files/TPC-TTIP-non-Papers-for-1st-Round-Negotiations-June20-2013.pdf> – policy objectives seem strongly oriented towards regulatory simplification and speedier mutual recognition procedures between US and EU.

⁷⁵ The confidential nature of the negotiation process is raising a vibrant debate over the lack of transparency of the entire venture: see for example the EU Ombudsman press release 17/2014 of July 31, 2014, formally asking the Council and the Commission to grant access to TTIP documentation, available at <http://www.ombudsman.europa.eu/press/release.faces/en/54636/html.bookmark>. The debate resulted in the Commission’s release, on the 7th January 2015, of the EU negotiating texts for TTIP, available at <http://trade.ec.europa.eu/doclib/press/index.cfm?id=1230>.

⁷⁶ Alemanno A., “A Reality Check of TTIP: Beyond the Popular Account”, opinion for Euractiv.com of April 2014, available at <http://www.euractiv.com/sections/trade-industry/reality-check-ttip-beyond-popular-account-301443>.

⁷⁷ *Ibidem*: see also for a more comprehensive discussion Alemanno A., “The Transatlantic Trade and Investment Partnership (TTIP) and Parliamentary Regulatory Cooperation”, European Parliament Policy Report, Brussels, April 2014, available at <http://ssrn.com/abstract=2423562>.

⁷⁸ *Ibidem*.

regulated.

The thesis shall analyse how close cooperation mechanisms are already in place; the impact of TTIP would, as far as regulation goes, substantially build upon existing consolidated practices. This, in turn, calls for a comparative approach. While a thorough and exhaustive comparative analysis of the regulatory architectures of the US and the EU has been recently provided by Alemanno and Richard Parker,⁷⁹ this thesis attempts a slightly different analysis, focusing on general trends in the evolution of the pharmaceutical regulatory architecture of both markets to suggest common ground.⁸⁰

The analysis of the EMA and the FDA is meant to shed light on a three-layered evolution of pharmaceutical regulation that is common to the US and the EU albeit within different institutional architectures. The first phase is the acquisition of ever-greater independence by such agencies and what can be referred to as ‘bodies of expertise’ *vis à vis* political institutions, both in the policy-making and in the decision-making stages. The second phase, a direct consequence of the first one, consists of the creation and consolidation of significant asymmetry between the formal distribution of power among political institutions and agencies, and the substantial exercise of said power. The third phase is the shift to the global arena. Here the focus is on the dichotomy between the transnational nature of the regulatory process and the domestic design of the regulatory frameworks leading to marketing approval.

The third transnational player taken into account in the descriptive process is the ICH, as the guidelines produced within its framework have a decisive impact in transnational regulatory practices (paving the way for regulatory cooperation quite similar to that suggested above regarding the potential impact of TTIP). Understanding the extent to which the current structure of this international forum is fit to achieve the goal of harmonising regulatory standards is critical to assessing the quality and safety of a

⁷⁹ Alemanno A., Parker R., “Towards Effective Regulatory Cooperation under TTIP: A Comparative Overview of the EU and US Legislative and Regulatory Systems”, Report to the EU Commission (DG Trade), available at http://trade.ec.europa.eu/doclib/docs/2014/may/tradoc_152466.pdf, concluding that despite major institutional differences, regulatory mechanisms share common essential goals in the pursuit, for example, of transparency; for a study on comparative administrative law see the essential Rose-Ackerman S., Lindseth P.L. (eds), *Comparative Administrative Law*, Edward Elgar, 2011.

⁸⁰ Other fields of risk regulation have ventured into EU-US comparisons to grasp the multi-faceted array of options stemming from diverse institutional designs that share similar goals and regulate similar products. For instance see the essential contribution by Geraint Howells on tobacco regulation and litigation across the Atlantic: Howells G., *The Tobacco Challenge*, Ashgate, 2011.

transnational approval procedure. Chapter II is therefore dedicated to the description of the FDA, the EMA, and the ICH.

Describing the institutional setting of the major transnational players is propaedeutic to the investigation of a series of crucial issues. The thesis questions the extent to which regulatory compliance is substantially fulfilled in case of multi-local production/testing. Is the current regulatory system fit to deliver the highest level of knowledge relevant to the assessment to be made? Are there institutional and cultural differences that structurally hinder the possibility of achieving harmonisation of regulatory standards, which could in turn produce a coherent and commonly understood transnational regulatory practice?

The substance of these issues is the core of the following chapter III, which investigates the potential for ‘gaps’ in scientific knowledge multi-locally produced. While chapter III was originally meant to contain a series of in-depth case studies, very limited access to essential information necessitated a significant reshaping of the argument, which is now focused on aggregate numbers rather than specific cases.⁸¹ This structure is no less effective in demonstrating the magnitude of the transnational regulatory practice in pharmaceutical pre-marketing approvals, and in proposing a series of substantial shortcomings. Nonetheless, data accessibility raises more general concerns about the transparency and accountability of the system at large. The pharmaceutical regulatory framework of pre- and post-marketing scrutiny is conceived to ensure the safety and efficacy of marketed products. The fact that crucial information is barely accessible questions *per se* the ability of the system to deliver the expected result, or to do so in the optimal way⁸² – at the very least, major concerns remain unanswered for lack of information.⁸³

Chapter IV shifts the focus from substance to procedure, questioning the deficiencies (or absence *tout court*) of mechanisms of participatory democracy at the stage

⁸¹ See section 1 of chapter III on the structural difficulties in accessing data.

⁸² As accurately explained by Steven Shavell, the definition of “optimal” varies considerably depending on the perspective one decides to adopt in analysing the system: see Shavell S., “The Optimal Structure of Law Enforcement”, 36 *Journal of Law and Economics*, 1993. The final section of this chapter is dedicated to making the study’s perspective explicit, the focus being on consumer safety.

⁸³ While the new EU regulation on access to clinical trials will certainly have a positive impact, its design seems to miss the centrality of transnational regulatory practices: see the discussion in chapters III and IV.

of law-making (which at first sight could appear as the natural balance to a system that is structurally interest-biased towards the industry, such as the ICH). The chapter will analyse the cases of ICH Guideline E6 on Good Clinical Practice (GCP) and E9 on the Statistical Principles for Clinical Trials (SPCT) to propose some conclusions on the model of governance and alternative sources of legitimacy of pharmaceutical regulation.

After examining the regulatory system's substantial issues and participatory shortcomings, chapter V moves to the levels of safety effectively achieved by the regulatory system. The analysis focuses on a series of case studies to uncover the results of the pre-marketing approval system, and the ability of post-marketing monitoring mechanisms to react promptly to emerging safety issues. In comparison to pre-marketing data, post-marketing surveillance data is significantly easier to access, therefore allowing for product-specific studies (to maintain coherence with the analysis on chapter III, general statistics will also be provided).

The second part of the thesis moves from the executive to the lens of the judiciary. As common features are identified in regulatory evolution, and solid regulatory cooperation mechanisms are already in place (and possibly on the verge of being significantly strengthened), the thesis maintains the comparative perspective adopted in the first part to explore the reactive mechanisms of the EU and US in the face of damages and regulatory failures.⁸⁴ Chapter VI attempts a descriptive overview of the role of courts in pharmaceutical litigation in the selected markets, while the subsequent chapters VII, VIII, and IX undertake an analysis somewhat mirroring that proposed for the executive, examining the ability of the judiciary to address substantial issues related to the quality and accessibility of scientific knowledge forming the basis of risk-benefit assessments, courts' participatory mechanisms, and their overall success in delivering product safety and addressing highly complex technical issues. Breaking down the contentious points, the analysis should help shed light on the following questions:

⁸⁴ The role of courts is a distinctive feature of the US, where the judiciary has through litigation traditionally performed a strong regulatory role. While the EU has traditionally maintained a different and less litigious attitude, recent trends suggest a move towards an "adversarial legalism" or "Eurolegalism" that is progressively bringing US and EU closer in their attitudes towards judicial complementarity of regulatory schemes. See Kelemen R.D., *Eurolegalism*; and Kelemen R.D., "Eurolegalism and Democracy", *Journal of Common Market Studies* 50, 2012.

1. Can courts play a role in the management of pharmaceutical products in terms of introducing transparency and coherence as regards the quality, relevance, and nature of scientific knowledge? In other words, can courts go beyond pure cost-benefit assessments, deferential to regulatory decisions, and enter the realm of uncertainty with value-based judgments?

2. Can courts act as a democratic agent? Can they act as a proxy for participatory democracy which appears to be lacking at a transnational level through accessible national enforcement mechanisms?

3. What are the opportunities for courts to deliver consumer safety (and if so, to go beyond the specific case and influence policy-making, which entails a broad understanding of the concept of ‘regulatory compliance’)?

What is essentially asked here is whether courts, and specifically *national* courts, can act as legitimating actors in a regulatory framework that embraces the market state idea: can ‘judicial governance’ provide a ‘social balance’ in terms of guaranteeing diffuse bottom-up control of the regulatory mechanism? If yes, judicial governance could be seen as a legitimating factor of the market state, embodying, short of participatory democracy, a democratically accessible agent. Courts could be conceived as reviewers of the regulatory process, which entails on the substantive side a review (direct or indirect) of actual standards as implemented, and on the procedural one a proactive role in favouring wider participation in harmonising standard-setting initiatives. A strong judiciary could strengthen its state’s protection of the social value of consumer safety – both in achieving the goals of the regulatory framework where there has been a safety failure (generally through compensation in a tort case), and in uncovering structural shortcomings of the regulatory system (for example through tackling the scientific knowledge issue raised above). Inevitably the thesis will touch upon the classic arguments against litigation and judges, which can be summarised in the question: “wouldn’t this be asking too much from the judiciary?” The discussion in chapters VII to IX should provide grounds for rebutting this scepticism.

The concluding chapter X evaluates the results of both parts of the thesis, executive and judiciary, pointing at positive (although limited) contributions of litigation outcomes, and proposes an enhanced ‘pedagogical role’ for courts. Turning back to the

question “are we asking too much from the judiciary?”, the core of the thesis suggests that the question should be reframed in a twofold way: first, *are we not asking too much from regulation under the current circumstances?*; and secondly, *are we asking judges the right questions?* While the law of torts and the processes of the courts have been widely accused of great inefficiency and for high transaction costs,⁸⁵ we take a perspective that departs from the analysis of cost to focus on the substantial issues at stake. Ultimately, if we accept a constructivist approach to law and science, according to which every regulatory assessment is fundamentally value-based,⁸⁶ the question is *who is best suited to make those value-based judgments?*

To summarise, the study (through its ‘descriptive bulk’ and the conclusions thereof) attempts an answer to the question: can judicial complementary governance provide social balance to the current regulatory framework for pharmaceutical product safety and its transnational imperatives?

6. A normative quest

Depicting the fundamental breaking points of pharmaceutical regulation invites critical reflection on the normative structure of the institutional design of the relevant system of rules. What is the *optimal structure of law enforcement*⁸⁷ in this field? Since the key issue in both regulatory and liability assessments related to pharmaceuticals is that of *relevant scientific knowledge*,⁸⁸ we claim that the legal framework should be shaped in the way

⁸⁵ See for example Polinsky M., Shavell S., “The Uneasy Case for Product Liability”, 123 *Harvard Law Review* 1437, 2010, suggesting that regulation and market forces have such an impact on firms in terms of incentives to product safety that product liability does not in fact exert a significant additional influence, while imposing additional costs that are ultimately borne by society at large. This argument will be touched upon when discussing the adequacy of courts in confronting pharmaceutical cases in chapter IX.

⁸⁶ The relationship between law and science produces something referred to as ‘regulatory science’ or ‘trans-science’. See chapter IX, and for a comprehensive discussion of the concept see Shapin S., *The Scientific Life*, and Jasanoff S., *Science and Public Reason*, Routledge, 2012.

⁸⁷ Shavell S., “The Optimal Structure of Law Enforcement”.

⁸⁸ The concept of relevant scientific knowledge is a rather complicated one. It is used in this context as a neutral term to describe the scientific information used in the assessment process. Normatively, we accept the definition suggested by Advocate General Tesauro in his Opinion to Case C-300/95 *Commission of the European Communities v. United Kingdom of Great Britain and Northern Ireland* ECR 1997, I-02649, in which he suggests that the concept should encompass all scientific knowledge “including the most advanced level of such knowledge, without any restriction as to the industrial sector concerned”. An excellent discussion of the political rather than purely scientific nature of the concept can be found in Jasanoff S., “Contested Boundaries in Policy-Relevant

that best promotes the availability of such knowledge.⁸⁹ Two major points should be made at this stage and subsequently investigated. First, regulation alone struggles to deliver the highest level of said knowledge, given the structural difficulties that we have suggested throughout this introduction, which will be developed through the description of institutional design confronted with the reality of regulatory practice. Second, if flaws in regulation hinder the availability of scientific knowledge that would be relevant to safety assessment, the question is *quid?* when one has to react to damage caused by a product that was imperfectly assessed. Is the relevant knowledge for a liability assessment that resulting from the regulatory assessment, or is the law of torts not limited to a retrospective investigation, and can it play instead a proactive role in unearthing relevant knowledge lost or undermined by the regulatory process? Such questions become more pressing in light of the transnational dimensions of the process.

The institutional framework governing regulation, confronting the issues raised by globalisation, currently reflects the delegation of states' regulatory powers to independent bodies, the legitimacy of which lies in their expertise. These bodies then interact at a transnational level. The de-nationalisation of regulatory procedures, combined with the progressive delegation of powers to technical bodies that are out of the traditional democratic circuits, poses both a problem of legitimacy and one of effectiveness of the regulations produced.

If we look for example at the ICH, the forum is exclusively conceived for regulatory agencies and industry representatives. The issue of access to information (both materially and intellectually) is tangible testimony of how *closed* the system is. Now if states progressively relinquish their authority in the field, and evolve (or regress) from a *rule-* and *decision-making* position to a *rule-taking* and *decision-receiving* position, what an individual (the consumer, ultimate target of the system's decisions) is left with in terms of engagement with the pharmaceutical system is his capacity/ability to react when the outcomes of the system's decisions affect him. In this sense the law of torts (and product liability in particular) constitutes a natural legal tool, as courts have the potential to implement a form

Science", 17 *Social Studies of Science* 2, 1997, pp. 195-230.

⁸⁹ For an interesting and still compelling discussion of the concept of "relevant knowledge" see Mildred M., "The development risk defence", in Fairgrieve D., *Products Liability in Comparative Perspective*, Cambridge University Press, 2005.

of surrogate democratic control⁹⁰ – although barriers to access in the EU compared to the US will require specific discussion.

How the regulatory and the litigation systems interact with each other will be examined. The hypothesis is that in a situation in which regulation is often the product of imperfectly harmonised rules, and non-transparent (if not potentially interest-biased) procedures, the law of torts can act as a helpful complement to ensure the achievement of the consumer protection goal of regulation. As for legitimacy, if the process of delegation/transnationalisation has reached the point of no return, the identification of forms of traditional democratic legitimacy appears difficult. One could think of mechanisms of participatory democracy for civil society that could ensure procedural transparency in the control of experts' technocratic regulation and decision-making.⁹¹ However, this would leave open the question of how to identify the representatives that are supposed to bring legitimacy to the process (a complex issue at all levels, *a fortiori* when the scene is transnational). The law of torts could be of great help here as the tool allowing the state to relocate its sovereignty through its individuals, empowering them to react individually to the decision-making outputs of a *closed system*.⁹² In other words, the pharmaceutical system appears to be shaped in such a way that the ultimate regulator has to be the individual himself: provided that the state protects its citizenry by giving it the means to actively react to processes that are otherwise not permeable. Essential agents of this relocated state sovereignty are national courts, whose oversight can potentially

⁹⁰ See the idea of “access justice” developed by Micklitz H.-W., “Social Justice and Access to Justice in Private Law”, *EUI Working Paper LAW*, No. 2011/02: the idea of justice through access (*Zugangsgerechtigkeit*) is based on the premise that it is for the sovereign actor (the EU in the paper's analysis) to grant access to justice to those who are excluded from the market or to those who face difficulties in making use of market freedoms. The idea is developed and adjusted to the field of pharmaceutical safety in chapter VIII.

⁹¹ Mechanisms of a Habermasian nature, see the essential Habermas J., *Between Facts and Norms: Contributions to a Discourse Theory of Law and Democracy*, MIT Press, 1996; and for a recent discussion Habermas J., “The crisis of the European Union in the Light of a Constitutionalisation of International Law”, *The European Journal of International Law* 23, 2012.

⁹² It appears indeed that there is here an ‘easy case’ for product liability. On the debate over the utility of product liability in the contemporary regulated world see again Polinsky M., Shavell S., “The Uneasy Case for Product Liability”, and *contra* see Goldberg J.C.P., Zipursky B.C., “The Easy Case for Product Liability Law: A Response to Professors Polinsky and Shavell”, 123 *Harvard Law Review* 1919, 2010, explaining how the former position is unsatisfying in terms of tort's deterrent and compensatory functions and victims' welfare. We will engage in this debate towards the end of the thesis, to plead for both an *easy case* (based on traditional goals of compensation and deterrence and the observed incremental impact on regulatory schemes) and a *complex case* (the pedagogical role of courts) for product liability in complementing and legitimating regulation.

perform a pedagogical role for regulators.⁹³

To summarise, in a context where the state is retreating from its classical top-down rule-making power, and is confronted with a transnational *closed and self-perpetuating system*, it may reinstate a form of bottom-up sovereignty by empowering individuals to exercise diffuse control of the decision-making process through litigious reactions to the decisions that affect them. The litigation process has also the potential to uncover relevant knowledge lost or undermined in the imperfections of the regulatory process.

The overview provided in this chapter has begun to uncover how pharmaceutical safety is characterised by the co-existence of elements of a fundamentally different nature, contributing to the creation of a very complex *interlegal* space.⁹⁴ Finding a balance among competing interests within this space is the delicate and challenging exercise to which this study attempts to contribute.

⁹³ The pedagogical role of courts *vis à vis* regulatory bodies is suggested by Jasanoff S., *Science at the Bar*, and will be developed in the concluding chapter X of the thesis.

⁹⁴ To use again the conceptual tool crafted by Santos B.S., *Toward a New Legal Common Sense*.

CHAPTER II

INSTITUTIONAL DESIGN OF WESTERN PHARMACEUTICAL REGULATION

A TALE OF TWO AGENCIES AND A TRANSNATIONAL REGULATORY NETWORK

This chapter analyses the development of both the FDA and the EMA in an attempt to expose the three fundamental phases in the evolution of pharmaceutical regulation previously described. To complete the analysis of the institutional design of Western pharmaceutical regulation, the analysis includes the phenomenon of the ICH as a transnational *sui generis* regulatory network, questioning its ability to introduce a reliable international regulatory structure, fit to effectively address the challenges created by the suggested three phases of regulatory evolution.

1. National development: the US Food and Drug Administration

The history of the FDA's regulatory powers begins with the story of a drug disaster, concerning *Sulfanilamide*, a compound imported to the United States from Germany in the early 1930s.⁹⁵ The original compound was mixed with a solvent, *diethylene glycol*, for the purpose of preparing the drug in syrup form, without any requirement for further tests or review of scientific literature on solvents. The result was a tragedy, resulting in over a hundred deaths in 1937.⁹⁶ As a reaction, in 1938 Congress approved the Food Drug and Cosmetic Act (FDCA) expanding FDA's oversight over the approval of

⁹⁵ The FDA was actually established in 1906 as a branch of the US Department of Agriculture with limited powers in reviewing food and drug labels. It was then moved to the Federal Security Agency in 1940, then to the Department of Health Education and Welfare in 1953, before settling in the Department of Health and Human Services in 1979.

⁹⁶ Cavers D.F., "The Food, Drug and Cosmetic Act of 1938: Its Legislative History and its Substantive Provisions", 6 *Law and Contemporary Problems*, 1939, pp. 2-42.

new drugs, and particularly over the ‘application’ a company was required to file in order to market a new product.⁹⁷ This initiative constitutes a first major preventive shift in the regulation of pharmaceutical marketing authorisation, as well as the first step in a progressive detachment between the US government and the FDA: the tests expected for the purposes of evaluating a drug’s safety were not specified in the statute, thus leaving considerable margins of manoeuvre to FDA officials in determining and negotiating testing protocols with the industry.⁹⁸ In this context, although the FDCA did not provide for any efficacy mandate, the agency started to resort to risk-benefit assessments, in so far as “a safe drug was one whose proposed use would benefit patients more than it harmed them”.⁹⁹

A subsequent turning point in US drug regulation happened in the 1960s, following another, and most likely the best known, major drug disaster, *Thalidomide*, which led to the birth of approximately 10,000 children with severe birth defects.¹⁰⁰ Although only seventeen cases were registered in the US, the seriousness of reports from Europe, and especially Germany, engendered a growing demand in public opinion for consumer protection and legislative action.¹⁰¹ As a result, substantial amendments to the FDCA were approved, authorising the FDA to set standards for every stage of a new drug testing. Government officials now had to approve a new drug before it could be consumed by patients.¹⁰² This shift was coupled with a great increase in the use of advisory committees and expert assessments, helping to protect the agency from potential attack on the ground that its decisions lacked scientific competence.¹⁰³ The reliance on scientific testing of new

⁹⁷ “If the secretary finds ... that the investigations ... which are submitted ... do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labelling thereof ... he shall, prior to the effective date of the application, issue an order refusing to permit the application to become effective”: U.S. Congress, “Federal Food, Drug and Cosmetic Act”, 75th Con. 2nd sess. (25 June 1938), Washington D.C., Government Printing office, 1938.

⁹⁸ See Marks H., *The Progress of Experiment: Science and Therapeutic Reform in the United States, 1900-1990*, Cambridge University Press, 1997, pp. 73-77.

⁹⁹ Marks H., *The Progress of Experiment*, p. 72.

¹⁰⁰ See McFadyen R., “Thalidomide in America: A Brush with Tragedy”, 2 *Clio Medica*, 1976, pp. 79-93; Daemrich A., “A Tale of Two Experts: Thalidomide and Political Engagement in the United States and West Germany”, 15 *Social History of Medicine*, 2002, pp. 137-158.

¹⁰¹ McFadyen R., “Thalidomide in America: A Brush with Tragedy”, pp. 79-93.

¹⁰² Which constituted “an important departure from the past”, when FDA officials were simply processing applications filed by drug manufacturers: see Daemrich A., *Pharmacopolitics – Drug Regulation in the United States and Germany*, The University of North Carolina Press, 2004, p. 30 ff.

¹⁰³ “The formidable array of expert advisory committees associated with the agency since the late 1960s testifies to its recognition that legitimation from the independent scientific community is

drugs appears for the first time in the 1962 statute.¹⁰⁴ In order to enforce these provisions, the FDA began not only to rely on advice from external scientific committees, but also to hire scientific experts as permanent agency officials.¹⁰⁵ With these provisions begins the first phase of our threefold regulatory evolution: that is the acquisition by the agency of independence from political institutions. With the FDCA allowing for ample margins of manoeuvre within a broad legal framework, the decision-making structure became arguably closer to policy-making, independent from the political sphere.

Around the mid-1970s, a strong anti-regulation movement emerged in response to the allegedly excessive precautionary model promoted by the 1962 statute, which was considered liable to unreasonably delay the accessibility of much needed new treatments,¹⁰⁶ a phenomenon known as “drug lag”.¹⁰⁷ Having been designed as a response to the *Thalidomide* case, the 1962 statute emphasised pre-market testing as the key feature to promote public safety when exposing consumers to a new treatment. However these critiques described the very same pre-market scrutiny as negatively impacting public health in terms of public suffering.¹⁰⁸ In response to increasing interest-based group pressure, representing both the industry and patients and seeking (for different reasons) prompt marketing of innovative pharmaceuticals, in 1988 the agency issued a series of regulations known as the “Treatment Investigational New Drug Regulations” (IND), the aim of which was to permit the distribution of unapproved investigational medicines to a limited target patient population suffering life-threatening conditions with the requirement that there should be a reasonably solid ground to consider the drug effective without exposing

indispensable to the success of its regulatory programs”: Jasanoff S., *The Fifth Branch*, p. 54.

¹⁰⁴ FDCA, as amended in 1962, §505(d).

¹⁰⁵ Jasanoff S., *The Fifth Branch*, p. 78.

¹⁰⁶ Several economic studies stress the decrease in new drugs approved since the adoption of the new legislation, raising a threat to innovation, Daemrich mentions for instance Grabowski H., *Drug Regulation and Innovation: Empirical Evidence and Policy Options*, American Enterprise Institute Press, 1976; Grabowski H., Vernon J., Thomas L., “Estimating the Effects of Regulations on Innovation: An International Comparative Analysis of the Pharmaceutical Industry”, 21 *Journal of Law and Economics*, 1978, pp. 133-163; Peltzman S., *Regulation of Pharmaceutical Innovation: The 1962 Amendments*, American Enterprise Institute Press, 1974.

¹⁰⁷ The term was first adopted by Wardell W., *Regulation and Drug Development*, American Enterprise Institute Press, 1975.

¹⁰⁸ A study linked several thousand deaths to delays in the approval of treatments such as *propanolol* and *practolol*: see Wardell W., “Introduction of New Therapeutic Drugs in the United States and Great Britain: An International Comparison”, 14 *Clinical Pharmacology and Therapeutics*, 1973, pp. 773-790.

patients to “significant additional risks”.¹⁰⁹

For the purposes of our analysis, it is essential to underline that these regulations, having a significant impact on public health in allowing the distribution of non-thoroughly-tested pharmaceuticals, were issued by the FDA and not Congress. Thus the agency proceeds to acquire regulatory power that goes beyond mere decision-making based on given regulations, and gains substantial policy and rule-making control. This phenomenon triggers the second phase of regulatory evolution, which we have described as the creation and consolidation of a significant asymmetry between the formal distribution and the actual exercise of power as between political institutions and administrative bodies. This phenomenon has been referred to as “administrative experimentalism” by Ladeur,¹¹⁰ with the aim of rationalising the discussion of the democratic deficit of bureaucracies. As will be discussed below, this study contests the ability of administrative experimentalism to effectively address the issues raised by the transnationalisation of administrative processes.

Following this trend, in the 1990s, pressured by the FDA’s increasingly autonomous initiatives, Congress enacted in 1992 the Prescription Drug User Fee Act (PDUFA) and in 1997 the FDA Modernization Act (FDAMA).¹¹¹ In adherence to the previous IND regulations, the new statutes included measures intended to reduce clinical study time, and provided for ‘fast-track’ procedures to quickly process drugs identified by the FDA as priorities.¹¹²

Ever since the adoption of these statutes, the FDA has been independently and regularly updating requirements and standards within the described framework.¹¹³ The increasing detachment of the agency from government oversight has been coupled with an expanding regulatory and decision-making power, culminating in 2006 with the adoption of the Requirements on Content and Format of Labelling for Human Prescription Drug

¹⁰⁹ IND, Federal Register 52 (22 May 1988), 19466.

¹¹⁰ As discussed extensively in chapter in chapter IV.

¹¹¹ PDUFA and FDAMA 21 U.S.C. § 356; 21 C.F.R. § 314.500.

¹¹² See Katin K. “The Prescription Drug User Fee Act of 1992 and the New Drug Development Process”, 4 *American Journal of Therapeutics*, 1997, pp. 167-172; Goldner L., “The U.S. Food and Drug Administration Modernization Act of 1997: Impact on Consumers”, 20 *Clinical Therapeutics*, 1998, pp. 20-25.

¹¹³ In 2007 another piece of legislation was introduced, the FDA Amendment Act (FDAAA), which, while acknowledging in form of law the autonomous regulatory initiatives undertaken by the FDA, did not introduce any major modification for the approval system: FDAAA, adding a new § 524 to the FDCA.

and Biological Products,¹¹⁴ in which the FDA sought to exempt its decisions from claims in tort law, unilaterally applying the “doctrine of implied preemption”.¹¹⁵ The system for marketing approval in the US had recently been subject to severe criticism in light of the several hundred deaths provoked by the latest major drug disaster, the Vioxx case.¹¹⁶ It has been argued that the preemptive shift of 2006 was in fact a reaction of the agency in an authoritative attempt to regain credibility, after the Vioxx case severely questioned its ability to ensure drug safety.

In light of this study’s goals, it must be underlined that the system is entirely *nationally* based. That is, the procedures in place for marketing approval are designed to be purely national. The existing regulatory framework is designed around the pre-marketing phase in a way that raises questions regarding the compatibility of its results with transnational practice. In other words, introducing the third phase of regulatory evolution, the focus moves to the adaptability of domestically designed (and, mostly, independently designed from political institutions) models and the shift towards global regulatory processes for marketing approval.

The assessment of a drug’s risk-benefit profile is the result of a procedure that is eminently characterised by a non-negligible degree of discretion on the part of the regulator. Throughout the pre-market review, the FDA evaluates a pharmaceutical product’s known risks and determines whether the product should be approved for marketing¹¹⁷ and which warnings should be included in the labelling¹¹⁸ in case of positive evaluation. The process of assessing risks and benefits is a case-by-case one. The following chapters will question the existing institutional setting of pharmaceutical regulation, analysing data that suggest a measure of caution against a typical legal attitude – mere deference to expert assessments – when facing highly technical matters. For now, it is

¹¹⁴ Requirements on Content and Format of Labelling for Human Prescription Drug and Biological Products, 71 Federal Register, 3922, 3934 (24 January 2006), 21 C.F.R. Pts. 201, 314, 601.

¹¹⁵ Because of the striking impact that such policy has on litigation, this issue is analysed and critically discussed in the second section of this chapter, dedicated to tort law rules.

¹¹⁶ To which we will come back both in the next section and mostly in the following chapters, as Vioxx is one of our case studies.

¹¹⁷ This decision is reached as a result of a risk-benefit balance, which will be explored in the following chapter with the help of selected case studies.

¹¹⁸ US Department of Health and Human Services, Report to the FDA Commissioner from the Task Force on Risk Management: “Managing the Risks from Medical Product Use – Creating a Risk-Management Framework”, 1999, available at <http://www.fda.gov/oc/tfrm/riskmanagement.pdf>, pp. 29-30.

worth recalling that a new product can undergo varying degrees of FDA scrutiny depending on originality and other factors. Standard drug approval proceeds in four steps:¹¹⁹

- Phase I seeks pharmacologic effects information and early evidence on effectiveness in a relatively restricted amount of healthy persons. About 20-80 subjects are usually involved in one or more of these trials.¹²⁰ The applicant typically begins this phase by testing several increasing dosages in the volunteers, to verify the safety and tolerability of the product and the pharmacokinetic profile (absorption, distribution, metabolism and excretion).

- Phase II measures several hundred closely monitored sick patients for the clinical effectiveness of the drug. This phase involves patients affected by the conditions for which the drug has been studied.¹²¹ Efficacy and safety are evaluated by continuing to test various dosage of the compound in patients.¹²²

- Phase III is characterised by multiple effectiveness and safety tests which form the basis for risk assessments and label warnings. It can involve fewer than a hundred patients in some cases or many thousands in others, depending on the target population and the endpoints being evaluated (on average tests involve 600 – 3000 patients). The drug is tested against a placebo. The trials are designed and powered to evaluate selected efficacy outcomes, not safety endpoints, although they can generate safety signals to pursue.¹²³

¹¹⁹ FDCA, as revised by the FDAAA, 2007, §505: the basic structure of the clinical trials does not differ substantially in its subdivision from that provided for in the EU market, although the details can be variable especially depending on the procedure to which a new product is subject (centralised or decentralised). We therefore present it here in its basic features: see Arbour M.E., *Sperimentazione dei Farmaci*, Pisa, 2006, p. 4 ff.

¹²⁰ FDA, *From Test Tube to Patient: The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, 4th Ed., 2006, available at <http://www.fda.gov/fdac/special/testtubetopatient/drugreview.html>.

¹²¹ CDER, FDA, DHHS, *The CDER Handbook*, 1998 (as amended in 2007), available at <http://www.fda.gov/cder/handbook/handbook.pdf>.

¹²² FDA, *From Test Tube to Patient*.

¹²³ It is interesting to observe how the efficacy test is undertaken against a placebo. We will see in the following that the EMA runs the same efficacy test against the most advanced drug of the same type already marketed. Such a major difference between the practice of the two agencies persists notwithstanding the ICH Guidelines on Good Clinical Practice (GCP), which were meant to harmonise, among other issues, the practice of clinical trials: see chapter IV.

- Phase IV involves delicate duties related to “post-marketing surveillance” through the mechanism known as *pharmacovigilance*. In particular, trials in Phase IV are aimed at monitoring safety through continuous scientific and technical data development after a new product is authorised for marketing. Phase IV studies can be required by regulatory authorities (as per the new legislation discussed in chapter V) but are most often undertaken by the marketing authorisation holder for competitive reasons, such as identifying new markets for the drug, new uses, or effective combinations with other drugs. As discussed in chapter V this type of safety surveillance is designed to detect rare and long-term adverse drug reactions (ADRs) using the target population as a dataset.

It has been calculated that clinical trials normally take two to ten years to complete their full cycle¹²⁴ depending on a series of variables.¹²⁵ An Institute of Medicine (IOM) study¹²⁶ describes the fundamental regulatory task of the specialised scientific committee of the FDA, the Centre for Drug Evaluation and Research (CDER), as being to follow experimental new medicines throughout each stage of the clinical trials, assessing their safety and efficacy along the way.¹²⁷ CDER experts can incentivise applicants to autonomously design product-specific strategies for post-marketing safety surveillance, as well as studies for the monitoring of potential development emerging risks, together with risk management strategies for the assessment of known risks. For assessment and further data collection purposes, the CDER in the late 2000s developed guidelines for marketing authorisation holders to develop Risk Minimisation Action Plans (RiskMAPs), with the aim of including a variety of “administrative activities to address risks that are known at the time of approval”.¹²⁸

¹²⁴ Chin R., Bairu M., *Global Clinical Trials*, Elsevier, 2012; PhRMA (Pharmaceutical Research and Manufacturers of America), *Pharmaceutical Industry Profile*, Report given in Washington D.C., 2006.

¹²⁵ Such as the rate of the event of primary interest, the length of patient follow-up, the staging of trials, and the difficulty of accruing patients: IOM, “Regulatory Authorities for Drug Safety”, in *The Future of Drug Safety – Promoting and Protecting the Health of the Public*, The National Academies Press, 2007.

¹²⁶ *Ibidem*.

¹²⁷ In particular, if during the trials the CDER “does not believe, or cannot confirm, that the study can be conducted without unreasonable risk to the subject/patient”, the committee can put the trial on hold until unsatisfactory elements such as adverse drug reactions (ADRs) are positively addressed: see CDER, FDA, DHHS, *The CDER Handbook*.

¹²⁸ See the regulated version of the RiskMAP initiative by the PDUFA, guidelines available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071616.pdf>; see also IOM, “Regulatory Authorities for Drug Safety”.

There are several technical conditions limiting the market reach of newly approved products that can be imposed by the agency at the time of approval.¹²⁹ Those conditions are mostly aimed at balancing the higher risks represented by drugs undergoing special procedures.¹³⁰ However such conditions have been described in a report by the Office of the Inspector General (OIG) as “difficult to put in place after the drug has been approved for marketing, as efforts to impose such conditions nearly always depend on voluntary compliance by the manufacturer rather than on the threat of withdrawal of the drug from the market as an imminent health hazard”.¹³¹

In 1992 PDUFA introduced additional difficulties for the FDA in exercising its authority before approval. A ‘fast-track’ approval process was made available for new drugs that “treat ... a serious or life-threatening condition and ... demonstrate the potential to address unmet medical needs for such a condition”.¹³² Aside from fast-track approval, under the ‘user fee’ provisions the FDA began charging companies to review applications in exchange for tighter adherence to deadlines. The FDA’s previous legal framework required application reviews to be done in 180 days; this schedule had proven almost impossible in regular practice.¹³³ PDUFA provisions on user fees have enhanced the rapidity of the agency’s decision-making, but the concern here is that the procedural rapidity needed to meet PDUFA goals may have made it even more difficult than before for CDER experts to investigate efficacy and safety issues thoroughly within the standard track.¹³⁴

¹²⁹ For example, distribution “limited to a specific medical specialty, distribution with required periodic screening to avoid contraindicated use, and distribution with mandatory enrolment in a registry”: DHHS, OIG, *FDA’s Review Process for New Drugs Applications: A Management Review*, OEI-01-01-00590, 2007, Washington D.C., OIG., reported by IOM, “Regulatory Authorities for Drug Safety”.

¹³⁰ See *infra* on the Prescription Drug User Fee Act (PDUFA).

¹³¹ DHHS, OIG, *FDA’s Monitoring of Post-marketing Study Commitments*, OEI-01-04-00390, 2008, Washington D.C., OIG, reported also by IOM, “Regulatory Authorities for Drug Safety”.

¹³² 21 U.S.C. § 356(a)(1); see also 21 C.F.R. § 314.500. For drugs that receive fast-track evaluation, the FDA may impose safety restrictions on the distribution or use of the drug, see 21 C.F.R. § 314.520; and may require post-approval studies, see 21 C.F.R. § 314.510; and “post-approval reporting of adverse events is much more closely monitored”, see O’Reilly, *Food and Drug Administration*, 4th ed., Thompson, 2014, pp. 13-83.

¹³³ IOM, “Regulatory Authorities for Drug Safety”.

¹³⁴ GAO, *Food and Drug Administration: Effect of User Fees on Drug Approval Times, Withdrawals and Other Agency Activities*, GAO-02-958, 2002; DHHS, OIG, *FDA’s Monitoring of Post-marketing Study Commitments*, OEI-01-04-00390, 2008.

The problematic issue the FDA is confronted with can be outlined as follows: the task of protecting consumer safety demands thorough pre-market scrutiny, but the FDA's parallel mandate to incentivise innovation creates a counter pressure. Responding to instances of various constituents seeking faster approval,¹³⁵ the FDA has established that pre-market approval can sometimes be based on “well-designed bench and/or animal testing” rather than clinical tests.¹³⁶ Moreover, according to the same guidelines, the FDA considers the extent to which measures such as post-marketing trials can substitute for pre-market scrutiny.¹³⁷

Now it is worth reporting a synthesised table depicting approval procedures in the decade 1995-2005,¹³⁸ bearing in mind that approximately 50% of applications undergo a user fee provision, and are thus *de facto* subject to fast-track approval.

Year	Fast-Track	Standard	Total
1995	10	19	29
1996	18	35	53
1997	9	30	39
1998	16	14	30
1999	19	16	35
2000	9	18	27
2001	7	17	24
2002	7	10	17
2003	9	12	21
2004	21	15	36
2005	15	5	20

This brief overview of the American pharmaceutical regulatory system provides perspective on two sets of issues. First, the system reveals itself to be fundamentally a domestic one, as it is conceived and designed as such. Second, certain elements suggest a measure of legitimate criticism as regards the pursuit of consumer safety. The generous

¹³⁵ As described *supra*.

¹³⁶ FDA, “The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry”, 2007, available at <http://www.fda.gov/cdrh/ode/guidance/1332.html>.

¹³⁷ *Ibidem*.

¹³⁸ Sourced from 2005 CDER Report to the Nation, available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/WhatWeDo/UCM078935.pdf>. Subsequent reports could not be retrieved.

input of third countries' data into the nationally consolidated FDA procedures has the potential to undermine the reliability of both the standard and (even more so) the fast-track approvals.¹³⁹ Standards have been subject throughout the 20th century to periodic review, driven either by precautionary or market-favouring pressures. However the situation appears considerably more problematic when confronted with the emerging transnationalisation of procedures, that is, the third phase of the evolutionary scheme proposed in the opening to this chapter: the tension between the domestic nature of the regulations in place, and the global shift of pre-marketing procedures, where the traditional US system of checks and balances is called into question.

2. A process of regional integration: towards the EU European Medicines Agency

The history of the creation and consolidation of the EMA as an independent agency is profoundly different from that of the FDA, succinctly depicted above. While the story of the FDA is a purely national one, the EMA introduces a supra-national element, as its origins and development walk alongside the process of European integration. Thus, in historical perspective, it is interesting to look at the process that led to the creation of the agency in the 1990s, to draw a parallel with the contemporary American developments that we have described.¹⁴⁰

The EU regulatory system for medicinal products is the oldest, most extensive, and most complex of any vertical product regulatory system, comprising a “very substantial body of Community legislation and case law”.¹⁴¹ It has been amended regularly since the first Directive was introduced in 1965 as a response to the *Thalidomide* tragedy¹⁴²

¹³⁹ Chapter III will explore the substantial intricacies of relying on foreign data.

¹⁴⁰ This short reconstruction owes very much to the works of Cuviller, “The Role of the European Medicines Evaluation Agency in the Harmonisation of Pharmaceutical Regulation”, in Goldberg R., Lonbay J. (eds), *Pharmaceutical Medicine, Biotechnology and European Law*, Cambridge University Press, 2001, p. 137, and Sauer, “New Drugs in the Global Economy: Risk Assessment and Risk Management in the EU and Co-Operation with the US”, Lecture delivered at the University of Pittsburgh, 13 November 2000.

¹⁴¹ Jacobs F.G., Advocate General, “Foreword”, in Goldberg R., Lonbay J., (eds), *Pharmaceutical Medicine, Biotechnology and European Law*; and Hodges C., *European Regulation of Consumer Product Safety*, Oxford University Press, 2005, p. 38.

¹⁴² See Teff H., Munro C.R., *Thalidomide: The Legal Aftermath*, Westmead Hants, 1976; Griffin J.P., Shah R.R., “The Development of the Control of Human Medicines in Europe from Classical Times to the Year 2000”, in Griffin J.P., O'Grady J., *The Textbook of Pharmaceutical Medicine*, 4th ed.,

(at which time only few countries already had regulatory systems in place),¹⁴³ contemporaneously with the 1962 strengthening of the FDA's prerogative in the US. Beginning in the 1960s, the EEC began to develop the concept of pre-marketing authorisation of new pharmaceutical products to ensure a minimum level of safety before distribution. A first step was taken with the approval of the framework Directive for the field in 1965.¹⁴⁴ The regulatory architecture it provided survived until 2001,¹⁴⁵ providing for a first European version of quality, safety, and efficacy assessment. Subsequently, based on that framework, in 1975¹⁴⁶ the Council drafted and issued the first legislation providing for the essential compulsory criteria of pharmaceutical scrutiny, based on a scientific evaluation grounding the pre-marketing authorisation process. Rules on pharmacological and toxicological testing and clinical trials were harmonised, together with the adoption of shared basic standards for national assessments by Member State (MS) authorities.¹⁴⁷

To promote collaboration between MSs and the EU Commission, in 1977 the Committee for Proprietary Medicinal Products (CPMP)¹⁴⁸ began its mandate. As an independent networking scientific committee, its functions were to foster harmonisation of assessment standards and to facilitate cooperation between national agencies and the EU Commission. The result of this initiative was to provide “the first EU-level forum for MSs representatives, from which grew networks of contacts”¹⁴⁹ among scientific experts

Routledge, 2002; Abraham J., Lewis G., *Regulating Medicines in Europe*, London, 2000.

¹⁴³ The US had introduced the FDCA in 1938, as we have seen in the previous section.

¹⁴⁴ Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products, 1965, OJ L369/65.

¹⁴⁵ In 2001 a new framework was approved under Council Directive 2001/83/EEC on the Community code relating to medicinal products for human use, 2001, OJ L311.

¹⁴⁶ Council Directive 75/318/EEC of 20 May 1975 on the approximation of the laws of Member States relating to analytical, *pharmaco-toxicological* and clinical standards and protocols in respect of the testing of proprietary medicinal products, 1975, OJ L147/1 and Second Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products, 1975 OJ L147/13.

¹⁴⁷ The time frame suggests that there was a ten-year gap between the moment the US introduced such legislation, and the moment the EU harmonised MS legislation on the topic. Such a gap is explainable by the fact that MSs began to legislate on the issue after the *Thalidomide* tragedy. This ten-year gap will however basically remain constant over time, as we shall see.

¹⁴⁸ Council Directive 78/420/EEC amending Second Directive 75/319/EEC on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products, OJ 1978, L 123/26.

¹⁴⁹ Sauer, “New Drugs in the Global Economy”.

coming from their authorities of origin in the MSs.¹⁵⁰ The supervisory responsibility of the MSs was addressed, identifying two key areas: inspections of testing and production sites, and pharmacovigilance duties. With the introduction of the concept of “manufacturing authorisation” national agencies were vested with the authority to ensure that each producer seeking marketing approval nominated a qualified agent responsible for batch release, thereby introducing the practice of ‘self-certification’.¹⁵¹

Alongside the legislation provided by the Directives, through the CPMP work, detailed scientific guidelines on drug testing emerged, contributing to the creation of a body of supplementary technical ‘soft law’.¹⁵² While not legally binding, these guidelines were very much an output of consultation and negotiation between the regulators and the regulated.¹⁵³ This is the beginning of that mechanism through which the regulators started, at a European level, to detach themselves from the traditional law-making power, gaining such a margin of manoeuvre in decision-making that they came closer to policy-making. To follow the scheme suggested for this chapter, this is the beginning of the first phase of regulatory evolution.

During the 1980s a significant trend started at the European level, combining and complementing harmonisation with mechanisms of mutual recognition of national rules and standards on the premise that they complied with EU legislation minimum requirements.¹⁵⁴ The reasoning was that even in the presence of full harmonisation of the rules, final decisions on marketing authorisations would always have to be made on a case-by-case risk/benefit assessment by MS authorities.¹⁵⁵ As a consequence, in the

¹⁵⁰ See also Wahlroos H., “Control of Medicines in the European Union and Drug Information”, in Valverde J.L., Weissenberg P., *The Challenges of the New EU Pharmaceutical Legislation*, 6 *Pharmaceutical Policy and the Law* 2005.

¹⁵¹ On the idea of self-certification see Cafaggi F., “Rethinking Private Regulation in the European Regulatory Space”, *EUI Working Papers – Law*, 13, 2006; Dehousse R., Joerges C., *Good governance in Europe's Integrated Market*, Oxford University Press, 2002; Black J., “Constitutionalizing self-regulation”, 59 *The Modern Law Review* 26, 1996.

¹⁵² As explained by Cuviller A., “The Role of the European Medicines Evaluation Agency in the Harmonization of Pharmaceutical Regulation” and Hodges C., *European Regulation of Consumer Product Safety*.

¹⁵³ The phenomenon is described by Howells G., *Consumer Product Safety*, Dartmouth, 1998.

¹⁵⁴ See Sauer, “New Drugs in the Global Economy”, and Cuviller A., “The Role of the European Medicines Evaluation Agency in the Harmonisation of Pharmaceutical Regulation”; for an account of the ‘trend’ see Rhodes R., *Understanding governance: Policy networks, Governance, reflexivity and accountability* (1997).

¹⁵⁵ Sauer, “New Drugs in the Global Economy”, and Cuviller, A., “The Role of the European Medicines Evaluation Agency in the Harmonization of Pharmaceutical Regulation”.

absence of unified decision-making procedures,¹⁵⁶ there would always be the potential for divergent assessments. To respond to the challenges of the Commission's White Paper on the completion of the single market,¹⁵⁷ and in response to the intricacies of conflicting regulatory outputs, the decision taken was to temporarily rely on mutual recognition of MS authorities' decisions.

Several initiatives among those suggested by the White Paper were dedicated to the pharmaceutical market, with a substantial delegation of power to the Commission for the harmonisation of pharmaceutical standards, and a higher reliance on comitology,¹⁵⁸ thus increasing the scientific committee's power in standard-setting and shaping of procedures.¹⁵⁹

The coordination of MS decision-taking was reinforced through the introduction of new legislation concerning biotechnology and other high-technology pharmaceutical products in 1987.¹⁶⁰ MSs took up the duty to process these types of pharmaceutical products in a somewhat collegial manner through the "concertation procedure".¹⁶¹

¹⁵⁶ See Cuviller A., "The Role of the European Medicines Evaluation Agency in the Harmonization of Pharmaceutical Regulation", p. 140, but this topic is addressed by several authors: see among others Feldschreiber P., "Marketing Authorisation", in Feldschreiber P. (ed.), *The Law and Regulation of Medicines*, Oxford University Press, 2008, 103.

¹⁵⁷ Commission of the European Communities, *Completing the Internal Market. White Paper from the Commission to the European Council*, Luxembourg, Office for Official Publication of the European Communities, 1985.

¹⁵⁸ See Sauer, "New Drugs in the Global Economy"; Cuviller A., 'The Role of the European Medicines Evaluation Agency in the Harmonization of Pharmaceutical Regulation'; and Schaefer G.F., "Linking Member State and European Administration – The Role of Committees and Comitology", in Andenas M., Tuerk A., *Delegated Legislation and the Role of Committees in the EC*, Kluwer, 2000.

¹⁵⁹ All industrially produced medicines were covered, including vaccines: Council Directive 89/342/EEC of 3 May 1989 extending the scope of Directive 65/65/EEC and 75/319/EEC and laying down additional provisions for immunological medicinal products consisting of vaccines, toxins or serums and allergens, 1989 OJ L142/14. Other measures introduced ranged from the authorisation procedures themselves, to issues of transparency in national pricing and promoting the rational use of medicines: Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating prices of medicinal products for human use and their inclusion in the scope of national health insurance systems, 1989, OJ L40/8; Council Directive 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use, 1992, OJ L113/1; Council Directive 92/26/EEC of 31 March 1992 concerning the classification for the supply of medicinal products for human use, 1992, OJ L113/5; Council Directive 92/27/EEC of 31 March 1992 on the labeling of medicinal products for human use and on package leaflets, 1992 OJ L113/8; and Council Directive 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use, 1992, OJ L113/13.

¹⁶⁰ Council Directive 87/22/EEC on the approximation of national measures relating to the placing on the market of high-technology medicinal products, particularly those derived from biotechnology, 1987, OJ L15/38.

¹⁶¹ Directive 87/22/EC. It should be noted that "products nationally authorised through the concertation

Alongside these provisions, the “rational use package” created a new line of obligations supplementing marketing authorisation, to be coupled with the existing Summary of Products Characteristics (SPC) – promoting the “rational use of medicines” by compiling in a standard form all information for consumers and advertisements.¹⁶²

Common ground was being established through the harmonisation and mutual recognition of basic rules. On this basis MSs and the Commission proceeded with the natural step forward, entailing a shift “from harmonisation of rules to harmonisation of decision-taking”,¹⁶³ a crucial step in the mechanism of detachment of the system from traditional lawmaking power.¹⁶⁴ This phenomenon, in our threefold scheme of pharmaceutical regulatory evolution, represents the move from phase one to phase two: that is from the acquisition of independence by expert bodies to the consolidation of a significant asymmetry between the formal distribution of power among the relevant actors, and its actual exercise by the prevalent one alone. The key move in this direction was the creation of a properly European marketing authorisation system with Council Regulation 2309/93/EEC, reinforced by the establishment of the EMEA (now EMA)¹⁶⁵ as an advisory body for the Commission. In agreeing to create the EMA, MSs began to *partially* renounce their sovereignty over the authorisation of medicines:¹⁶⁶ unlike the FDA, which is completely centralised, the EMA was defined as a ‘networking’ agency, networking with and supervising MS authorities. Alongside the inauguration of the EMA,

procedure were given a ten-year protection against a second applicant. This was particularly important at the time given the lack of harmonisation of patent protection across the Community”: see Cuviller A., “The Role of the European Medicines Evaluation Agency in the Harmonization of Pharmaceutical Regulation”, p. 141.

¹⁶² See Wahlroos H., “Control of Medicines in the European Union and Drug Information”, in *The Challenges of the New EU Pharmaceutical Legislation*, 6 Pharmaceutical Policy and the Law, 2005.

¹⁶³ See also Alder, “Roles and responsibilities of the Regulator”, in Feldschreiber P. (ed.), *The Law and Regulation of Medicines*, 73.

¹⁶⁴ See on the nature of this shift Rhodes R., *Understanding governance: Policy networks, Governance, reflexivity and accountability*; Teubner G., “Breaking Frames: the global interplay of legal and social systems”, 45 *American Journal of Comparative Law*, 1997, p. 149; Dehousse R., Joerges C., *Good governance in Europe's Integrated Market*, Open University Press, 2002; Joerges C., Teubner G., *Transnational governance*, Open University Press, 2004; Scott C., “Regulating constitutions”, in Parker C. et al., *Regulating law*, Open University Press, 2004, 226; Scott J., Trubek D., “Mind the Gap: Law and new approaches to governance in the European Union”, 8 *European Law Journal*, 2002, 5.

¹⁶⁵ Council Regulation 2309/93/EEC laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use, and establishing a European Agency for the Evaluation of Medicinal Products, OJ 1993, L214.

¹⁶⁶ A phenomenon that is increasing through time given the greater reliance on the centralised procedure that the EU pharmaceutical approval system is progressively showing, as suggested below.

the Regulation introduced the marketing authorisation architecture that is still in place with two alternative procedural mechanisms, centralised and decentralised.

The centralised procedure was, at its origin, compulsory exclusively for pharmaceutical products derived from biotechnology, and left as an option for other innovative products.¹⁶⁷ Since 2004,¹⁶⁸ the scope of the compulsory application of the centralised procedure has been progressively expanded and specified. In the centralised procedure a marketing authorisation application (MAA) must be made directly to the EMA for evaluation by the CPMP (renamed CHMP, Committee for Medicinal Products for Human Use, since 2001). The actual marketing authorisation is then issued by the Commission on the basis of the EMA's advice.¹⁶⁹ Once granted, a centralised marketing authorisation is valid throughout the whole EU. Post-marketing surveillance is now disciplined by the recently adopted Directive 2012/26/EU,¹⁷⁰ whereby the EMA avails itself of the network of national MS authorities to effectively perform pharmacovigilance.

The decentralised procedure was (and still is) based on the principle of mutual recognition of national authorisations between MSs as elaborated in the 1980s. While it was originally widely adopted for the majority of non-biotech new medicines,¹⁷¹ its use for innovative products is progressively diminishing. The procedure allows for a national marketing authorisation holder to extend the validity of his authorisation to one or more selected MS markets. Under this procedure the EMA functions as an arbitrator in the event that a MS refuses to recognise the validity of an applicant's authorisation. The main committee involved is the Coordination Group for Mutual Recognition and Decentralised Procedure – Human (CMDh),¹⁷² created in 2005 to mediate disagreements between MSs. If conciliatory attempts fail, the matter is referred to the CHMP for arbitration (the

¹⁶⁷ See Annex to Council Regulation 2309/93/EEC, OJ 1993, L214/1.

¹⁶⁸ Council Regulation 726/2004/EC laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ 2004, L 136/1.

¹⁶⁹ Note as set out below that the Commission never departs from the EMA's opinions.

¹⁷⁰ Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance (Text with EEA relevance), OJ 2012 L 299/1.

¹⁷¹ Sauer, "New Drugs in the Global Economy"; Cuviller A., "The Role of the European Medicines Evaluation Agency in the Harmonisation of Pharmaceutical Regulation".

¹⁷² See EMA, *Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh)*, available at <http://www.ema.europa.eu/ema/> under 'Committees'.

decision is then enforced by the Commission).¹⁷³

The creation of the EMA prompted the creation of new advisory committees of scientific experts, now directly participating in the preparatory phases of decision-making.¹⁷⁴ The most significant innovation at the time of the creation of the EMA was that scientific opinions adopted by advisory committees were now transformed into legally binding decisions by the European Commission.¹⁷⁵

Contrary to that of the FDA, the history of the creation of the EMA is eminently supra-national. It is the result of a remarkable effort of coordination. It must be recalled that at the time the first EU legislation was adopted in the field, almost no MSs had in place an autonomous legal framework for the regulation of medicines. The parallel development of national authorities and EU legislation in the field was a key factor in facilitating harmonisation of both rules and decision-making.¹⁷⁶ As we shall stress in the following sections, an ever-stronger move towards centralisation of procedures suggests that the EU can be considered as a highly integrated market in the pharmaceutical field, and that its legislation is *de facto* domestic in nature. This is the scenario in which the move to the third phase, the dichotomy between domestic regulations and global practice, becomes challenging.

The regulatory system of pharmaceutical product safety was extensively revisited in 2001, being subject to a substantial codification process, followed by a refinement in 2004.¹⁷⁷ This reform did not however change the peculiar feature of the EU pharmaceutical regulation model, which is the coexistence of two procedures. This situation, it will be recalled, is an inheritance of the absence of a central authority until the mid-1990s, which necessitated reliance on national authorisations granted by MS authorities and on the principle of mutual recognition among MSs.¹⁷⁸ While the 2001

¹⁷³ Both mechanisms, centralised and decentralised, are now disciplined by Council Directive 2001/83/EC on the Community code relating to medicinal products for human use, OJ 2001, L311/67.

¹⁷⁴ As provided by Council Regulation 2309/93/EEC of 22 July 1993, OJ L214.

¹⁷⁵ Sauer, “New Drugs in the Global Economy”; Cuviller A., “The Role of the European Medicines Evaluation Agency in the Harmonisation of Pharmaceutical Regulation”.

¹⁷⁶ Feldschreiber P., “The Structure and Function of Medicines Regulation in Europe”, in Feldschreiber P., *The Law and Regulation of Medicines*, 3.

¹⁷⁷ Council Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L311; Council Directive 2004/27/EC; Council Regulation 726/2004/EC.

¹⁷⁸ The regime was provided by Council Directive 65/65/EEC, and subsequent amendments. This situation, as suggested in the text, developed historically: when introduced, Directive 65/65/EEC

reform has not modified this coexistence, there is an apparent trend towards greater reliance on the centralised procedure,¹⁷⁹ reshaping the EU regulatory model in a centralised fashion and reinforcing the decision-making power of the CHMP. Although the committee's function is formally purely advisory, its decisions are in practice always conclusive, as there has not been a case where the Commission has departed from the committee's advice¹⁸⁰ in the formal decision-making process. The Commission here has become a decision-taker¹⁸¹ (a perfect example of what we refer to as phase two of the regulatory evolution, the asymmetry between form and substance: the formal power to adopt legally binding decisions remains within the Commission, but never has the Commission rejected the EMA committee's opinions).

Among the factors that demonstrate this trend towards centralisation, we should mention on the one hand the greater coherence of such a model in the context of a European single market, and on the other hand the fact that the operational history of the mutual recognition system has proven itself to be less than satisfactory,¹⁸² as it reveals inefficiencies and anomalies in the delivery of safety. First, the two procedures differ in their wordings insofar as they regulate the risk-benefit assessment that leads to marketing approval. While the centralised procedure leads to denial of marketing authorisation when

called for the introduction of national authorisation systems, which was arguably all that could be contemplated either in practice or politically at the stage, and reforms to the mutual recognition procedures have slowly but gradually been introduced since then, for example under Directive 87/22/EEC, which required that applications for high technology products had to be referred to the CPMP for an opinion before a (national) marketing authorisation could be granted. The centralised procedure introduced by Regulation 2309/93/EEC was effectively established on a trial basis, restricted to certain categories of product which are the subject of expansion, see the following note. Whereas some authors suggest that the system is outdated and about to be abandoned altogether, see Hodges C., *European Regulation of Consumer Product Safety*, p. 40, others suggest that it is still of great importance and should be taken as a model for an international marketing approval procedure, see Purnhagen K., "The Challenge of Globalisation in Pharmaceutical Law – Is an International Drug Approval System Modeled After the European System Worth Considering?", *Food and Drug Law Journal* 63, pp. 644-645.

¹⁷⁹ Since the creation of the EMA in the 1990s, the mandatory scope of application of the centralised procedure has been regularly expanded: for a comprehensive summary see <http://www.docstoc.com/docs/30996001/EMA--Marketing-Authorization>.

¹⁸⁰ Once again we can observe a progressive detachment of the decision-making power, captured by the scientific experts, similarly to what we have observed with the CDER in the FDA's system.

¹⁸¹ See Krapohl S., *Risk Regulation in the Single Market – The Governance of Pharmaceuticals and Foodstuffs in the European Union*, Palgrave Macmillan, 2008, p. 83: "Although the expert committee was set up as an advisory body for the evaluation of medicinal products, it became a rule-setting actor on its own during the 1990s".

¹⁸² The need for a more consistent use of the centralised procedure is stressed by Peter Feldschreiber, arguing that the decentralised procedure does not seem to have been achieving its functional scope of facilitating pharmaceutical distribution in the EU market but has rather created confusion: see Feldschreiber P., "Marketing Authorization", pp. 103-111.

“it appears that the applicant has not properly or sufficiently demonstrated the quality safety and efficacy of the product, or that the particulars and documents are incorrect”,¹⁸³ the mutual recognition procedure sanctions denial only where “it is clear that the risk-benefit balance is not considered to be favourable, that its therapeutic efficiency is insufficiently substantiated by the applicant, or that its qualitative and quantitative composition is not as declared”.¹⁸⁴ More fundamentally, what introduces an element of uncertainty in the mutual recognition system is the definition of risk as provided by Directive 2001/83/EC, article 28. According to this provision, risk related to the use of medicinal products is defined as “any risk relating to the quality, safety or efficacy of the medicinal product as regards the patients’ health or public health; any risk or undesirable effects on the environment”. According to subsequent article 28a, the risk-benefit balance consists of “an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks as defined in point 28”. A risk is, therefore, “any risk”.¹⁸⁵ As a recent study conducted among EMA regulators has shown, there is no clear practical understanding of what a risk is under the current regulatory framework for the EU pharmaceutical market.¹⁸⁶ And here is the major argument *contra* the decentralised procedure. Since conceptions of risk vary considerably within a single regulatory authority, the degree of variation is consistently increased by involving multiple regulatory authorities.

The EMA was therefore born as a networking agency, with explicit centralised powers only for a limited number of cases, but partly because of the operational failure of the decentralised model, it has acquired a significantly more centralised position. We argue that this creates a strong domestic framework (the EU) which is however vulnerable when permeated from the outside, for the very reasons that suggested a shift from decentralised to centralised procedures *within* the EU.

¹⁸³ Council Regulation 726/2004/EC, art. 12.

¹⁸⁴ Council Directive 2001/83/EC, art. 26.

¹⁸⁵ The lack of clarity regarding such a key notion as ‘risk’ in the regulatory process that leads to market approval suggests that the CHMP’s *de facto* decision-making power is in fact a policy-making power, as the regulation’s vagueness leaves room for substantial discretion on the part of the decision-makers.

¹⁸⁶ Phillips L.D., “EMA risk-benefit project”, LSE, presented at the British Institute of International and Comparative Law, 29 September 2010, pointing out how among EMA regulators 51 different definitions of ‘risk’ were collected.

3. Attempts at transnational harmonisation of regulatory procedures

Whereas the European and American regulations for pharmaceutical approval are developed within a precise legal framework, at an international level the situation is substantially different, very much dependent on negotiating processes rather than clear regulations, notwithstanding the ever-increasing transnationalisation of production and testing. We have suggested throughout this chapter that there is a dichotomy between domestically designed regulatory frameworks and transnational regulatory processes. We will describe the reality of this phenomenon in the next chapters. Here, in the chapter dedicated to the institutional design of pharmaceutical regulation, we give an account of an informal and hybrid body, equally constituted by public regulators and private companies, which represents the most advanced attempt to date to overcome the issues raised by said dichotomy.

Over the past twenty years, regulators and the pharmaceutical industry began to find a common interest in attempting to eliminate unnecessary delays in the global development and distribution of new treatments, and more generally in harmonising the requirements for drug approval at a transnational level, an initiative consistent with the global nature of the pharmaceutical market. Following the WHO International Conference of Drug Regulatory Authorities (ICDRA),¹⁸⁷ held in Paris in 1989, the regulatory authorities of the US, the EU, and Japan founded the permanent International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Its mission is to “make recommendations towards achieving greater harmonization in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration”.¹⁸⁸

The ICH is organised as a hybrid public/private transnational regulatory network; its Steering Committee is the main body, which can issue legally non-binding guidelines for its members.¹⁸⁹ Decision-making is structured as a negotiation process among the

¹⁸⁷ The ICDRA provides drug regulatory authorities of WHO Member States with a forum to meet and discuss ways to strengthen collaboration: see http://www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra/en/index.html.

¹⁸⁸ See ‘ICH vision’, at <http://www.ich.org/about/vision.html>. For a scholarly overview see Berman A., “The Role of Domestic Administrative Law in the Accountability of IN-LAW: The Case of the ICH” in Pauwelyn J., Wessel R., Wouters J. (eds.), *Informal International Lawmaking: Mapping the Action and Testing Concepts of Accountability and Effectiveness*, Oxford University Press, 2012.

¹⁸⁹ As will be discussed in chapter IV, the nature of those guidelines is controversial. It has been argued

members of the committee, the composition of which is worth recalling: EMA (together with a representative from the Commission), the FDA, Japan Ministry of Health, European Federation of Pharmaceutical Industries and Associations (EFPIA), JPMA (Japan Pharmaceutical Manufacturers Association), and PhRMA (Pharmaceutical Research and Manufacturers of America).¹⁹⁰ These six founding members are the main actors in the negotiation process that leads to the adoption of harmonised guidelines. The WHO, the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the European Federation of Pharmaceutical Industries and Associations (EFPIA), and Health Canada (the Canadian regulatory authority for food and drug safety) have permanent seats on the committee as non-voting observers.

The harmonisation activity of the ICH can take four different procedural shapes: the development of a new guideline (Formal ICH Procedure), the creation of questions and answers to assist the implementation of a new guideline (the Q&A Procedure), the revision or modification of existing guidelines (the Revision Procedure), and the addition of standards to existing guidelines and recommendations (the Maintenance Procedure).¹⁹¹ The output of ICH work is translated into domestic regulatory frameworks through policy documents that escape the normal agency processes of adoption.¹⁹²

Analysing a decade of work in the year 2000, the ICH announced that it has been “successful in achieving harmonization, initially of technical guidelines and more recently on format and content of registration applications”.¹⁹³ Topics discussed by the forum range over the entire terrain of drug testing, from *pharmacokinetics* to clinical trials. Activity in the second decade has been significantly and progressively less frenetic, and only a few

that they possess a *de facto* binding effect, the major example being that the E6 ICH guidelines on Good Clinical Practice have been largely copied in the draft of Directive 2001/20/EC on Good Clinical Practice, as noted by Krapohl S., *Risk Regulation in the Single Market*, p. 84, Purnhagen K., “The Challenge of Globalisation in Pharmaceutical Law”, p. 638, and Katsikas D., “International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceutical Products”, in Hale T., Held D. (eds), *Handbook of Transnational Governance*, Polity Press, 2011. However, *how* these guidelines are implemented, not only in the EU but in all ICH constituencies, is quite problematic.

¹⁹⁰ These are associations representing R&D pharmaceutical industry, and accordingly companies engaged in the development of new drugs; the industry in general is not included.

¹⁹¹ On the harmonisation procedures see the ‘ICH structure’ section of the ICH website, www.ich.org; for a full and detailed account of the ICH organisation see Purnhagen K., “The Challenge of Globalization in Pharmaceutical Law”, pp. 637-640.

¹⁹² The issue is tackled in chapter IV.

¹⁹³ International Conference on Harmonization, Steering Committee, “The Future of ICH – Revised 2000”, Statement on the occasion of the Fifth International Conference on Harmonization, 9 November 2000, available at <http://www.ifpma.org.ichl.html>.

guidelines and standards are in various stages of the ICH process at this time.¹⁹⁴ Whereas consensus was reached quickly in a series of non-controversial areas,¹⁹⁵ others are proving much more difficult to harmonise, mainly the specific standards for clinical trials. And on this observation it is now necessary to raise some critiques.

First, the composition of the decision-making body raises an immediate problem in terms of legitimacy: the negotiation process excludes representatives of patients, while it provides for a strong inclusion of representatives of industry (international and regional). As has been fairly observed, “the pharmaceutical industry is involved in the harmonization process right from the beginning and is able to influence the ICH directly from its heart as a member of its main working unit”.¹⁹⁶ Moreover, we have explored in the course of this section how regulatory authorities are shaped, and how their evolution shows a progressive acquisition of independence by technical experts, coupled with the consolidation of an asymmetry between formal distribution and actual exercise of power. The issue of legitimacy has been addressed as regards such authorities, in their domestic dimension, in such a way that the lack of democratic legitimacy of their rule-making power is compensated via a “credible commitment”,¹⁹⁷ a form of output-based legitimacy that will be thoroughly explored in chapter IV.

An argument that must be raised here can be drawn from the EMA experience. The shift from a decentralised process to an increasingly centralised authority has been depicted in the previous section. The country of origin, and legal and cultural background, of each MS authority has proven so influential as to pose concrete obstacles to an effective and efficient use of the decentralised procedure. The inability of the ICH to tackle substantial issues in clinical trial requirements, going beyond mere procedural standards,¹⁹⁸ over a period of more than twenty years of activity, is a clear sign of the same issues at a transnational level: participants in a regulatory network are tied to their authorities of origin in a way that poses a structural obstacle to the creation of common

¹⁹⁴ As at May 2015, only three are undergoing a process of open consultation: see <http://www.ich.org/products/open-consultation.html>.

¹⁹⁵ Such as basic guidelines on drug quality standards, necessary toxicity tests, and expectations for good clinical practice: a full account is available at <http://www.ich.org/products/guidelines.html>.

¹⁹⁶ Purnhagen K., “The Challenge of Globalization in Pharmaceutical Law”, pp. 638-639.

¹⁹⁷ Majone G., *Regulating Europe*; Krapohl S., “Credible commitment in Non-Independent Regulatory Agencies: A Comparative Analysis of the European Agencies for Pharmaceuticals and Foodstuffs”, *European Law Journal* 10, 2004. See discussion in chapter IV.

¹⁹⁸ See chapter III.

thinking, and consequently common interest.¹⁹⁹

Aside from the fields where it fails to find a common ground for consensus, when it does, the local implementation of guidelines issued by the ICH displays significant variations, calling into question the effectiveness of their harmonisation potential. For example, the Good Clinical Practice (GCP) guidelines as outlined by the ICH²⁰⁰ have been fully implemented in the EU,²⁰¹ including the parallel Good Manufacturing Practice (GMP) guidelines, whereas the two issues are considered separate and independently regulated in the US.²⁰² The GCP guidelines, however, were intended to integrate the two aspects, as “the authors of this clinical guideline had an excellent appreciation for the ramifications of inadequate manufacturing or packaging on the clinical program”.²⁰³ This example is quite effective to reinforce the criticisms raised above, as the GCP guidelines are often used in the literature as a paradigmatic example of successful harmonisation from the ICH.²⁰⁴

In a global environment in which harmonisation of regulatory procedure is struggling to overcome resistance from competing regulatory styles, a transnational regulatory practice via the ICH is undoubtedly well in place.²⁰⁵ That said, the ICH model begs serious questions in terms of the legitimacy of its procedures and outputs, a legitimacy which does not appear to be balanced via a ‘credible commitment’. We have analysed the process of detachment which led, over the past decades, to the acquisition by technical experts in the form of committees and by officials of national and regional

¹⁹⁹ In this perspective it is striking to observe that the main obstacle to harmonisation between the EU and the US in particular, has been for this whole period, and remains, the placebo versus best competitor in the market discrepancy between the standards applied by the two agencies. This shows how the very idea of a risk-benefit assessment is intimately linked to attitudes that are, even in a globalised world, still eminently local.

²⁰⁰ ICH, *Tripartite Harmonised Guidelines – Guideline for Good Clinical Practice E6* (R1, 10 June 1996), available at <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>.

²⁰¹ Directive 2001/20/EC, OJ 121/34 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

²⁰² See the FDA guide to regulations on GCPs, available at <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090259.htm>; and the separate guide to regulations on GMPs, available at <http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/CurrentGoodManufacturingPracticesCGMPs/ucm110877.htm>.

²⁰³ Simmons J., Bernstein D., “Navigating Differences between FDA and EMA for Regulatory Compliance During Drug Development”, *BioPharm International*, September 2006, 2; and see also ICH E6 Guidelines, GCP, section 5.14.

²⁰⁴ Krapohl S., *Risk Regulation in the Single Market*, p. 84, and Purnhagen K., “The Challenge of Globalization in Pharmaceutical Law”, p. 638.

²⁰⁵ We have briefly analysed in chapter I the transnational approval procedure that led to the marketing of the A-N1H1 vaccine; this topic will be thoroughly discussed in chapter III.

regulatory authorities of substantial rule- and decision-making power (what we have described as phases one and two of the regulatory evolution). The lack of legitimacy of those expert bodies can arguably be overcome via different legitimating factors, built around the concept of output-based legitimacy and credible commitment to the mandates they serve. However these factors do not seem to apply at a transnational level (the issue described in phase three of the evolution as a dichotomy between domestic regulations and global processes). The expanding existence of a transnational regulatory practice not only brings back the issue of legitimacy, but also raises a pressing concern in terms of consumer safety. The shortcomings we have briefly reported generate a level of uncertainty that calls for a detailed analysis of transnational procedures for risk-safety assessments. In the absence of traditional legitimacy, and in the presence of substantial elements of uncertainty, there is a need for a form of control on the outcomes of transnational but incompletely harmonised regulatory procedures.

The next three chapters will ‘question’ the system as described in this chapter. Chapter III will propose an analysis depicting the extent of the transnational phenomenon in pharmaceutical regulation; chapter IV describes the rules involved and their source of legitimacy; and chapter V attempts to evaluate the results in terms of safety delivery, that is, evaluating the output that supposedly legitimises the system *ex post*.

CHAPTER III

QUESTIONING THE INSTITUTIONAL DESIGN 1

QUALITY, PROVENANCE, AND COMPATIBILITY OF SCIENTIFIC DATA

The institutional design described in the previous chapter is now to be questioned on the basis of empirical data. The first stage of this inquiry involves analysing the quality, provenance, and compatibility to receiving markets of scientific data resulting from outsourced clinical trials. This is because clinical tests on human subjects constitute the paramount and primary source of the scientific knowledge incorporated in risk assessments for marketing authorisations.

The first section explores difficulty in accessing data for qualitative research. The second moves to a description of the phenomenon of clinical trials outsourcing. The third section proposes a series of critical elements suggestive of potential structural biases in data quality and reliability. The concluding remark posits that the uncertain scenario resulting from the analysis carried out throughout the chapter raises questions about the quality of pre-market assessments, and thus, a legal question of substantial regulatory compliance with the requirements of the receiving markets.

1. Structural difficulties in accessing data: (un)balancing conflicting interests

The idea of this chapter was originally quite simple: to evaluate the substance of the standards involved in the assessment of a new product for its marketing authorisation. For this purpose, the scheme to be followed would have been one that identifies where and when the product was marketed; where and when the product was tested; and whether there were significant differences in the regulatory requirements of the testing countries compared to the receiving markets. The goal of this scheme would have been to assess

whether or not there is ambiguity in the scientific data relied upon for marketing authorisation, and if so, whether such ambiguity is a consequence of unclear or blurred regulatory requirements rather than unavoidable scientific uncertainty.

The most effective way to put such a test into practice is to select a few products and trace back their history from discovery, to testing, to marketing: an exercise that would give clear indications and favour firm answers to the proposed questions. However, as simple and clear as such a structure would have been, its practical realisation has proven to be impossible save at the cost of gross approximation. The reasons are many-fold and will be touched upon in this chapter as well as in the following ones. This section analyses the failure of this experiment and suggests how failing to retrieve conclusive data is not simply a serious obstacle to scientific research (not to mention public access to information at large) but also, and perhaps more importantly, gives reason for considerable concern about the quality and exchangeability of assessments made within different social and legal frameworks.

The essential obstacle here was access to data. A crucial piece of information needed to undertake the type of case study originally conceived is the location of clinical trials, the pivotal ones in particular.²⁰⁶ Such information has been however, as will be discussed, extremely difficult if not impossible to obtain.²⁰⁷ Reports on clinical trials are, in most cases, partial and difficult to interpret when it comes to identifying the precise location of the trials. In an attempt at following the original scheme, the study was supposed to focus on three products: *Rofecoxib* (Vioxx), *Rosiglitazone* (Avandia) and *Drospirenone* (Yasmin and Yasminelle). The questions proposed were, as indicated above, the following: where was the product marketed? Where was the product tested in order to obtain marketing authorisation? Were there straight-up contrasts between the regulations of the testing and receiving markets, or ambiguities in the methods of cross-reference and

²⁰⁶ *Pivotal* clinical trials are to be considered those that form the basis for agencies' assessments that the medicine to be marketed is safe and effective for its intended use.

²⁰⁷ For literature on the difficulty of accessing critical data see among others Rennie D., "When Evidence Isn't: Trials, Drug Companies and the FDA", 15 *J.L. & Pol'y* 991, 2007; Göttsche P.C., Jorgensen A.W., "Opening up Data at the European Medicines Agency", *British Medical Journal* 342, 2011, d2686; on the recent developments that will improve the accessibility of data in the EU see Bonini S. et al., "Transparency and the European Medicines Agency – Sharing of Clinical Trial Data", *New England Journal of Medicine* 371, 2014; Strom B.L. et al., "Data Sharing, Year 1 – Access to Data from Industry-Sponsored Clinical Trials", *New England Journal of Medicine* 371, 2014; for a US development see Zarin D., Tse T., "The Proposed Rule for U.S. Clinical Trial Registration and Results Submission", *New England Journal of Medicine* 372, 2015.

interpretation of foreign data? And what margin of appreciation was given to the data receiver in order to fit the foreign data into the receiving regulatory framework? The key aim was to explore the basic issue raised in the Introduction to this work: whether or not transnational testing is fit to comply in substance with the safety requirements of the receiving markets, in other words, fit to ensure real regulatory compliance.²⁰⁸

The reasons for choosing the aforementioned products were simple: all have been distributed in the markets this work focuses on, all have been tested transnationally,²⁰⁹ and all caused severe unexpected harm to patients once on the market.²¹⁰ Further, since one of our selected markets of investigation is the EU, another criterion was to pick products covering both the centralised and the decentralised procedure.²¹¹ Interviews with medical assessors of the EMA and former FDA officials confirmed that those products are all good representatives of the development of regulatory safety issues and well worth investigating.²¹²

The research was carried out in the following way. The first sources consulted were public records and databases, namely the online databases of the relevant agencies. At a second stage, said agencies were directly contacted for specific information missing from the public record. Subsequently the sponsors, that is the involved pharmaceutical industries, were approached, and finally NGOs active in the field. The results were distinctly underwhelming.

It has not been difficult to figure out where the products were marketed, as that information is easily retrievable from agency and industry records.²¹³ The problematic part begins once the research moves on to the second step, that is, where the products have been tested. While there are significant indications in the scientific debate that all three

²⁰⁸ We will discuss in the next chapters IV and V how if an issue exists on the effectiveness side, that is in terms of output, then from a legitimacy angle output-based legitimacy is necessarily weakened.

²⁰⁹ Further details will be provided in the following section of this chapter.

²¹⁰ The issue is developed in chapter V, which discusses the safety outcome of the regulatory procedures.

²¹¹ *Rosiglitazone* was approved via the centralised procedure, while *Rofecoxib* and *Drospirenone* underwent the decentralised one, with respectively the UK and the Netherlands as reference MSs.

²¹² Personal interviews with Dr. Peter Feldschreiber, senior medical assessor of MHRA and EMA consultant, and Dr. Jur Strobos, senior medical assessor of the FDA.

²¹³ For the US see the products approval chart available at <http://www.fda.gov/Drugs/default.htm> (type the name of the product in the ‘search drugs’ area); for the EU, Public Assessment Records are available at <http://www.ema.europa.eu/> (type the name of the product in the ‘search for medicines’ area).

have undergone tests in third countries,²¹⁴ access to the details of the clinical trial sites is simply not to be found.

First, as recalled, the investigation covered the public records. Starting with *Rosiglitazone* (brand name Avandia), here are the results.²¹⁵ As regards the US, the clinical trials register²¹⁶ lists a grand total of 40 trials, 35 of which completed (only 5 showing results), 2 active, 1 recruiting, 1 terminated, 1 unknown.²¹⁷ None of the listed trials however precedes the date of approval for the US market of Avandia, which was May 1999.²¹⁸ As for the EU, the authorisation came a year later, in July 2000. However, the EMA's Public Assessment Reports (PAR) are completely silent as regards the location of trials.²¹⁹ The European clinical trials register²²⁰ lists only 59 trials, all subsequent to the date of approval and conducted within the EU and EEA.²²¹ Information on pivotal trials for marketing authorisation is accordingly not accessible through public records. The story of *Rofecoxib* (brand name Vioxx) and *Drospirenone* (brand names Yasmin and Yasminelle) is essentially similar: the only difference being that, in the EU, since these two products were approved under the decentralised procedure, the difficulty in accessing the relevant data for the research arose when searching the British²²² and Dutch²²³ agencies' public records.

The next step consisted of a direct request to the agencies to access data on clinical trials location. The results of this search were more interesting. While none of the correspondence with US public officials examining the request can be quoted, the essential contents of the exchanges can be reported.²²⁴ The FDA, through the CDER Division of Drug Information, suggested that such data, for all three products, should be requested

²¹⁴ This will be further discussed in section 2, but see specifically Schipper I., Weyzig F., "Ethics for Drug Testing in Low and Middle Income Countries: Considerations for European Market Authorization", *SOMO*, February 2008; Chin, R., Bairu M. (eds.), *Global Clinical Trials – Effective Implementation and Management*, Elsevier Academic Press, 2011.

²¹⁵ As at May 2015.

²¹⁶ Available at <http://clinicaltrials.gov/>, self-described as the official "registry and results database of publicly and privately supported clinical studies of human participants conducted around the world".

²¹⁷ See US clinical trials register, *ibidem* (type '*Rosiglitazone*' in the 'search for studies' area).

²¹⁸ See FDA *Letter of Approval* ND 21-071, available in the drugs database at www.fda.gov (type 'Avandia' in the 'search drugs' area).

²¹⁹ See EMA European Public Assessment Record on Avandia, reference EMA/230001/2010, available at www.ema.europa.eu.

²²⁰ Official EU clinical trials register of the EMA, available at <https://www.clinicaltrialsregister.eu/>.

²²¹ See *ibidem*.

²²² Medicines and Healthcare Products Regulatory Agency (MHRA), see <http://www.mhra.gov.uk/>.

²²³ Dutch Medicines Evaluation Board (CGB-MEB), see <http://www.cbg-meb.nl/>.

²²⁴ It is worth noting that the correspondence is personal and unofficial, and the agency remained silent when asked (several times) for an official statement on the matter.

directly from the sponsors, as it is considered Confidential Commercial Information and therefore belongs to the sponsors under the American Freedom of Information Act.²²⁵ The agency itself reviews the data but does not retain records of it. As for the EU, the discourse is similar but complicated by the centralised versus decentralised procedure factor. In the case of Avandia, approved through the centralised procedure, an information request was sent to the EMA. The response was more elaborate than that received from the FDA, but inconclusive for the identification of decisive trial locations outside of the US and EU zone: it only included “a list of clinical trials, which may be considered pivotal with regard to the initial marketing authorisation of Avandia”,²²⁶ the location of all of which is either in the US or in the EU.²²⁷ Whether or not such a list is exhaustive of the trials upon which the risk assessment for the EU marketing authorisation was based is hard to tell as no further information was provided, but there are ample independent indications that suggest Avandia was indeed tested in third countries.²²⁸ Multiple personal communications with EMA officials, which again are not to be quoted, confirm that significant portions of clinical trials, especially in Phase III,²²⁹ were outsourced to countries other than EU Member States or the US, but that those locations and sites are covered by stringent confidentiality agreements.²³⁰ As for Vioxx, since it was first authorised in the UK, the request was sent to the British MHRA. The exact reply cannot again be quoted, on the explicit request of the respondent, but in essence it reveals that the agency has very little information on the countries and sites in which the clinical studies were conducted, and only very limited records of a single study conducted in “South America”, with no further specification. This is because the MHRA shreds on a regular basis trial records after 15 years, thus losing critical information and data.²³¹

²²⁵ See US Freedom of Information Act (FOIA) 5 U.S.C. 552, Exemption 4 “Confidential Business Information”.

²²⁶ EMA/188255/2012 – 20 March 2012 – Human Medicines Development and Evaluation, response to request for information on clinical trials RFI-2012 No 01-309.

²²⁷ *Ibidem*.

²²⁸ See Ridley D.B., Grabowski H.G., Moe J.L., “Developing Drugs for Developing Countries”, *Health Affairs* 25, no.2, 2006, pp. 313-22; Dickersin K., Rennie D., “Registering clinical trials”, *Journal of the American Medical Association* 290, 2003, p. 516; Koski G., Nightingale S.L., “Research Involving Human Subjects in Developing Countries”, *New England Journal of Medicine* 345, 2001, pp. 136-38.

²²⁹ Phase III is characterised by multiple effectiveness and safety tests which form the basis for risk assessments and label warnings. An average of 1,000 to 3,000 patients are exposed to the experimental treatment in this phase, which is essential for the safety and efficacy final assessment.

²³⁰ Personal communications with EMA contract agent and CHMP official, December 2011–March 2012. Unfortunately no further details can be shared.

²³¹ MHRA shreds clinical trials data upon which it takes the decision to authorise a product for marketing

Moreover, personal communications with one MHRA senior official confirmed that Vioxx approval was supported by scientific evidence of third country provenance.²³² Yasmin and Yasminelle were first approved by the Dutch agency. Here the response to the access to information request was a straight negative, as the location of trials is “classified information” in order to preserve the “privacy of participants”.²³³

The third step consisted of contacting the sponsors directly. The only sponsor to reply, after repeated information requests, was GlaxoSmithKline, sponsor of Avandia. The information provided was irrelevant to the location of trials, and limited to data available on both US and EU clinical trials registers and general (public) prescribing information for Avandia.²³⁴ Neither Merck (for Vioxx) nor Bayer (for Yasmin and Yasminelle) responded at all.

Finally, when asked about clinical trial locations, NGOs active in the field of pharmaceutical product safety simply referred to the public records.²³⁵ The Cochrane Collaboration²³⁶ made reference to its database, however no further data than those available from agency websites could be found.

The issue of access to clinical trials data is old and has been substantially explored especially in scientific literature.²³⁷ The problem being that, given the proprietary nature of

15 years after the product enters the market. See Götzsche P.C., Jorgensen A.W., “Opening Up Data at the European Medicines Agency”: “Under MHRA record management policy, all application files and data for licences are held for 15 years. After this period, files are destroyed unless there is a legal, regulatory, or business need to keep them, or unless they are considered to be of lasting historic interest.”

²³² Personal communication with MHRA senior medical assessor, September 2010–March 2011. Unfortunately no further details can be shared.

²³³ Personal communication with Ben Klijn, Communications Department – Dutch Medicines Evaluation Board, 8 February 2012. Attempts were also made with the French and Italian agencies; both responses referred the requester to the Reference Member State (RMS) authorities. The Swedish and Danish agencies did not refer to the RMS authorities but denied to release the information as it constitutes “trade secrets”.

²³⁴ Personal Communication with Christine Henning Pharm. D. – Senior Medical Information Scientist – GlaxoSmithKline, 1 February 2012, Ref. 11491752.

²³⁵ Several NGOs were contacted, including three very prominent ones in the field of pharmaceutical monitoring: Health Action International (www.haiweb.org/), the independent review Prescrire (<http://english.prescrire.org/>), and SOMO, the Center for Research on Multinational Corporations (<http://somo.nl/>), in several personal email communications. Each response referred to public records.

²³⁶ See the database at <http://summaries.cochrane.org>.

²³⁷ Within such literature, among the most recent examples see: Mathieu S. et al., “Comparison of Registered and Published Primary Outcomes in Randomized Control Trials”, 302 *JAMA* 9, 2009, pp. 977-984; Wieseler B. et al., “Still Waiting for Functional EU Clinical Trials Register”, 342 *BMJ*, 2011, d3834; Prayle A.P. et al., “Compliance with Mandatory Reporting of Clinical Trials Results on

such data when arising from privately sponsored trials, regulators are either not in possession of the relevant documentation or confront significant obstacles when they elect to publish it. Three very recent cases from the General Court of the European Union (GC) give an uncontroversial *aperçu* of how the balancing of competing interests is interpreted when it comes to publication of trials data. In these cases, a third party was seeking access to documentation that formed part of a marketing authorisation submitted to the EMA by private sponsors, regarding the trial testing of three drugs, claiming a right to access to documents pursuant to Regulation 1049/2001.²³⁸ The EMA, in Decision EMA/24685/2013 of 13 January 2013, granted access to such documents and as a result was sued by the sponsors. With its Orders of the Court T-44/13, T-73/13 and T-29/13,²³⁹ the GC ordered immediate suspension of the EMA's decision based on the fact that the relevant data had not yet been made available to the public, *de facto* sanctioning, on the one hand, a wide discretionary power of the industry in controlling the publication of data, and on the other hand, at a more general level, a strong tendency to uphold commercial confidentiality or individual privacy over transparency and access to information.

The situation is certainly evolving in a positive direction after the adoption of a new EU regulation on clinical trials that tackles the issue of access.²⁴⁰ The regulation introduces a Portal for EU clinical trials where publication is compulsory,²⁴¹ but only, according to article 1, for clinical trials conducted “in the Union”. The new legislation therefore appears to leave the issue of publication of trials conducted in third countries untouched, except where special reporting duties are provided for.²⁴² As pointed out in

ClinicaTrials.gov: Cross Sectional Study”, 344 *BMJ*, 2012, d7373; Chan A.-W., “Out of Sight but not Out of Mind: How to Search for Unpublished Clinical Trial Evidence”, 344 *BMJ*, 2013, d8013. A more journalistic but comprehensive and well documented overview of the issue can be found in Goldacre B., *Bad Pharma*, Fourth Estate, London, 2013, Chapter I “Missing Data”.

²³⁸ Regulation (EC) 1049/2001 of the European Parliament and of the Council of 30 May 2001 regarding public access to European Parliament, Council and Commission documents, OJ L 145, 31/05/2001 pp 0043-0048.

²³⁹ Case T-44/13 Order of the President of the General Court, 29 April 2013, *Abbvie v EMA*, OJ C 189, 29.06.2013, p. 24–25; Case T73/13 Order of the President of the General Court, 25 April 2013, *InterMune v EMA*, OJ C 189, 29.06.2013, p. 25–25; Case T-29/13 Appeal of EMA against decision in Case F-29/13 *Drakeford v EMA*, OJ C 202, 30.06.2014, p. 27 – see chapter VII for a discussion of the cases and their appeal.

²⁴⁰ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.05.2014, pp. 1–76; see the discussion in Bonini S. et al., “Transparency and the European Medicines Agency – Sharing of Clinical Trial Data”; and Strom B.L. at al., “Data Sharing, Year 1 – Access to Data from Industry-Sponsored Clinical Trials”.

²⁴¹ Regulation (EU) No 536/2014, arts. 80-82.

²⁴² See *ibidem*, arts. 42 and 53.

scientific literature,²⁴³ the wording of the new requirements remains uncertain as regards the extent of the Confidential Business Information (CBI) exemption, and only a close monitoring of actual enforcement practice will clarify if and to what extent such provisions are effective.²⁴⁴ And a major limitation of the new legislation is its non-applicability to already marketed products, which suggests that the real impact of the new regulation will be perceivable as for marketed drugs only in some ten to fifteen years from now.

Clinical trials location thus remains a closely protected trade secret, of which agencies are either not in possession or not at liberty to disclose publicly. From a legal perspective, we contend that if data are insufficient to follow the testing of a product into the details of the location of pivotal clinical trials (which is necessary information to evaluate the compatibility of data in testing and receiving markets), this uncertainty alone is sufficient to question substantial compliance with the safety requirements of the receiving market. The following sections set out the reasons for this claim.

2. Outsourcing of clinical trials to third countries – a widespread phenomenon

If a close study on specific cases is not possible given the confidential nature of the data that would be required, the second-best option is analysis from a macro-level perspective. The globalisation of clinical trials is a major subject for scientists and sociologists.²⁴⁵ While specific cases are difficult to penetrate, scientists, epidemiologists and agency civil servants are more at liberty to discuss the phenomenon at large, that is, without entering into the details regarding single products (or only partially doing so). This is evident in the abundant literature on the topic of clinical trial outsourcing, in the form of studies commissioned by agencies themselves, and more prominently, discussions in

²⁴³ Toussaint B., “EU Clinical Trials Regulation”, 381 *the Lancet* 9879, 2013, pp. 1719-1720; Götze PC., “Deficiencies in Proposed New EU Regulation of Clinical Trials”, 345 *British Medical Journal*, 2012, e8522.

²⁴⁴ See also Rizzi M., “Simple Safe and Transparent? - Preliminary Reflections on the Adoption of a New EU Regulation on Clinical Trials”, *European Journal of Risk Regulation* 4, 2013, p. 534 ff.

²⁴⁵ The major sources for this section and the following one will be the leading medical journals *the Lancet*, the *New England Journal of Medicine (NEJM)*, and the *Journal of the American Medical Association (JAMA)*; the work of Drs Richard Chin and Menghis Bairu, leading US clinical trials experts; and the work of Peter Feldschreiber, senior medical assessor at MHRA and consultant for the EMA.

top medical journals such as the *New England Journal of Medicine* (NEJM), the *Journal of the American Medical Association* (JAMA), the *British Medical Journal* (BMJ), and the *Lancet*. Based on both such scientific literature and personal (often anonymous) interviews, sociologists have been trying to work on the subject as well, tackling it from various perspectives, mainly the selection criteria for patients in clinical trials or how, through the outsourcing of clinical trials to middle- and low-income countries, said trials become integral to public health and quality of healthcare in developing contexts.²⁴⁶ These sources are of paramount importance for the present study, together with the work of NGOs.²⁴⁷ Their analysis is generally not comprehensive for single products, but by tackling in depth specific steps or issues in the life-cycle of a medicine, they contribute significantly to the better definition of a bigger picture.

We contend that legal scholarship has by contrast been neglecting this aspect of pharmaceutical safety regulation,²⁴⁸ and we posit that reinstating a comprehensive legal discourse is essential to the better fulfilment of public and individual health protection goals.

The conclusion of the previous section, having described the impossibility of in-depth qualitative analysis on a case-by-case basis as regards testing locations, is that the widespread outsourcing of clinical trials for marketing authorization is a source of uncertainty sufficient *per se* to question compliance with the receiving markets' requirements. The first element to take into account in support of such a claim is the extent of the outsourcing phenomenon.

It is difficult to trace a linear picture of the growth of the phenomenon through time. Reports tend to be a little erratic and often only cover specific periods or provide partial coverage:²⁴⁹ the numbers that are available constitute a 'guesstimate', often

²⁴⁶ The phenomenon is well explored in Petryna A., *When Experiments Travel – Clinical Trials and the Global Search for Human Subjects*, Princeton University Press, 2009.

²⁴⁷ Again, the most significant share will come from the work of Health Action International (www.haiweb.org/), the independent review Prescire (<http://english.prescire.org/>), and SOMO, the Center for Research on Multinational Corporations (<http://somo.nl/>).

²⁴⁸ As chapter II attempts to illustrate, the legal discourse is still very much linked to a national or regional perspective, and does not seem to fully appreciate the consequences of outsourcing for regulatory compliance on the one hand, and on the other hand the issue of legitimacy regarding the procedures allowing such outsourcing (explored in the following chapter IV).

²⁴⁹ The issue is explored by prominent anthropologist Adriana Petryna in several contributions, including Petryna A., "Clinical Trials Offshored: On Private Sector and Public Health", *BioSocieties* 2, 2007, p. 21, noting that an estimated 50,000 clinical trials are active around the world, but that these

conservative.²⁵⁰ In this light it has, significantly, been argued that ambiguities in numerical estimates are by themselves proof of a “global field of experimental activities whose true scope is largely unknown”.²⁵¹ Ten years ago, senior medical assessors suggested that “major barriers to a comprehensive repository of clinical trials” included “industry resistance [and specifically resistance to allowing full disclosure of the entirety of clinical studies conducted per product], the lack of a funding appropriate for a serious and sustained effort, lack of a mechanism for enforcement of policies, and lack of awareness of the importance of the problem”.²⁵² The observations made in the opening of this chapter, together with several testimonies from the scientific environment, suggest that progress is still needed on the topic. Indeed, there is evidence that only an average of one in 37 trial studies reported to the FDA for new drug applications gets published.²⁵³ No such data is available for the EMA – although for EU-based trials, the new Regulation should end the struggle.

Despite the unrefined contours of the issue, it is worth taking a close look at the available figures on the globalisation of clinical testing, as these are significant notwithstanding their incompleteness. The section proceeds with a review of the US and EU numbers.

The EU figures suggest the following. A report published by the EMA in 2013 provides interesting overviews of the distribution and number of patients, investigator sites and pivotal clinical trials included in Marketing Authorisation Applications (MAA)

estimates “differ dramatically” depending on the sources.

²⁵⁰ For instance, the number of 50,000 active clinical trials, suggested *supra*, is the result of a study by the Thomson CenterWatch in Boston, a non-profit survey center. According to Petryna, *ibidem*, “50,000 is a ‘guesstimate’ – ‘very conservative’ – in large part because of the drug reviewers’ lack of knowledge of the number of experiments informing a new drug application”.

²⁵¹ Petryna A., *When Experiments Travel*, pp. 89-98.

²⁵² Dickersin, K., Rennie, D., “Registering clinical trials”, p. 518.

²⁵³ See Wilson J.B., Gomez-Panzani E., “United States Regulations”, in Chin R., Bairu M. (eds.), *Global Clinical Trials*. It is also worth recalling that registered trials constitute only a fraction (estimated roughly around 50%) of the overall amount of trials. This study only focuses on registered trials as these are the ones upon which marketing authorisation is granted. However, the absence of a clear registry of all clinical trials undertaken by sponsors is a significant public health issue worth investigating. See also MacLean C.H., Morton S.C., Offman J.J. et al., “How Useful are Unpublished data from the FDA in Meta-Analysis”, 56 *Journal of Clinical Epidemiology*, 2003, pp. 44-51. A strong case for data publication has been made recently by Zarin D., Tse T., “The Proposed Rule for U.S. Clinical Trial Registration and Results Submission”. An analysis of the virtues of patient-level data accessibility can be found in Nisen P., Rockhold F., “Access to Patient-Level Data from GlaxoSmithKline Clinical Trials”, *New England Journal of Medicine* 369, 2013.

submitted to the EMA during a period spanning January 2005 to December 2011.²⁵⁴ The data presented shows that 62% of the overall patient population in pivotal clinical trials submitted to the EMA during the relevant period were from non-EU countries, comprising 37.3% from the ROW region (Rest of the World, comprising Africa, Middle East/Asia/Pacific, Australia/New Zealand, Central/South America, CIS, Eastern Europe non-EU), and 31.5% from North America (US and Canada).²⁵⁵ The number of patients recruited in the EEA is substantially decreasing, and the major contributors are Finland, Germany and Poland.²⁵⁶ By contrast, the number of patients recruited in the ROW area, primarily middle- and low-income countries, is proportionally growing. China, Costa Rica, Philippines, Japan, Brazil, Russia, Thailand, and South Africa had a range of 120 to over 200 patients recruited per pivotal clinical trial per country in MAAs submitted to the EMA in the relevant period.²⁵⁷ The overall trend as regards clinical trial site increases in ROW countries (and especially developing countries) is substantially proportionate to that of patients.²⁵⁸ A further element of interest is the number of patients per site as registered in submitted clinical trials reports to the EMA for MAA. The average for the ROW area is significantly higher than in other regions. The EU/EEA/EFTA registers 13 patients per site,²⁵⁹ North America 10, while the ROW averages 17 (the peak being Africa with 23, followed by Central/South America with 20).²⁶⁰ These rates are particularly significant, as the following sections will uncover, because of the structural difficulties in quality control by investigators in developing country sites.

As for the US, the numbers have been growing rapidly as well, but the calculation is conducted in a slightly different way. A report from the Office of the Inspector General (OIG) of the Department of Health and Human Services (DHHS) shows that as of 2008,

²⁵⁴ The data is extremely partial as, first, not all products for the considered period are included, and secondly, most trials are excluded as not published and/or not registered. See the full report, EMA, *Clinical Trials Submitted in Marketing Authorization Applications to EMA: Overview of Patients recruitment and the Geographical Location of Investigator Site*, Doc. Ref. EMA/INS/GCP/676319/2012, 11 December 2013, available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf.

²⁵⁵ See EMA, *ibidem*, p. 9, Table 2.

²⁵⁶ See EMA, *ibidem*, p. 22, Figure 12.

²⁵⁷ See EMA, *ibidem*, p. 23, Figure 13.

²⁵⁸ See the study carried out by the EMA member of the Working Group on Third Country Clinical Trials, Altavilla A., "Ethical Standards for Clinical Trials Conducted in Third Countries: The New Strategy of the European Medicines Agency", *European Journal of Health Law* 18, 2011, pp. 65-67.

²⁵⁹ The number is inflated by the higher average number of patients per site in the new European countries (19 per site) compared to older western European countries.

²⁶⁰ EMA, *Clinical Trials Submitted in Marketing Authorization Applications to EMA*, p. 21, Figure 11.

80% of marketing applications for new medicines (NDA) approved by the FDA contained data on clinical trials conducted outside the US.²⁶¹ According to that report, more than 50% of both patients and trial sites involved in these applications had non-US provenance.²⁶² These numbers are extrapolated taking into account only the applications with sufficient information to determine whether the data were non-US. Again, in light of the recalled issues of accessibility and ownership of data on trial locations, these numbers are to be considered partial and conservative.²⁶³ Of the more than 57% of patients in NDAs who were from non-US sites, a significant portion came from the EU/EEA/EFTA zone (with 14%), whereas the ROW region accounted for over 29%.²⁶⁴ The numbers are collated from 121 applications approved by the end of fiscal year 2008, and cover patients enrolled in trials conducted over the previous 10 years, that is since 1998.²⁶⁵ A different study reports that, as at the end of 2007, over one third of the overall trials submitted for NDAs that year (157 of 509) had been conducted solely outside the US, and that a majority of investigation sites (13,521 of 24,206) were outside the US, most of them located in ROW regions.²⁶⁶

Taking the figures of North America and EU/EEA/EFTA zones together, there appears to be a growing trend since 1998 of both patients and clinical trial sites external to these areas and mostly from the ROW region. Precise statements of the number of trials and patients per trial over the last 15 years would be little more than ‘guesstimates’ (as recalled, only a fraction of registered clinical trials are published, and only about half the overall trials are registered). There is however one figure that is uncontroversial and significant. If we look at the number of non-US/non-EU clinical investigators, the percentage of these investigators identifiable in MAA and NDA applications in the relevant period grows from 15% in 1998 to 31% in 2008.²⁶⁷

²⁶¹ See Levinson D.R., “Challenges to the FDA’s Ability to Monitor and Inspect Foreign Clinical Trials”, DHHS - OIG, 2010, p. 10.

²⁶² See *ibidem*.

²⁶³ See the discussion *supra* in section 1 and the Thomson CenterWatch Survey as reported in Petryna A., “Clinical Trials Off-shored”, p. 21.

²⁶⁴ See Levinson D.R., “Challenges to the FDA’s Ability to Monitor and Inspect Foreign Clinical Trials”, p. 12, Graph 1; and Chin R., “Background”, in Chin R., Bairu M. (eds.), *Global Clinical Trials*, pp. 4-6.

²⁶⁵ See Levinson D.R., “Challenges to the FDA’s Ability to Monitor and Inspect Foreign Clinical Trials”, p. 14, Graph 3.

²⁶⁶ See the explanation of these numbers in Glickman et al., “Ethical and Scientific Implications of the Globalization of Clinical Research”, *NEJM* 360, 8, 2009, pp. 816-823.

²⁶⁷ The result is extrapolated from the data on clinical investigators in the OIG study of D.R. Levinson,

Even if the general observations above are grounded on partial and, time-wise, somewhat erratic numbers, there is consensus among both the scientific community and the regulators (two figures often problematically overlapping, as suggested in chapters I and II) that the phenomenon of off-shoring of clinical trials to third countries for developing/testing medicines for which an NDA or an MAA is submitted in the US or the EU market is a consolidated and growing reality.²⁶⁸ The reasons for this shift are numerous and shall be summarised below.

The first reason is savings in cost and time. This aspect can be broken down into three elements. The primary element is the actual cost-saving that off-shoring trials to ROW regions implies. India and South Africa are growing clinical trial hubs for this reason, especially for Phases II and III of clinical studies.²⁶⁹ In a 2008 interview with the *Harvard Business Review*, an anonymous executive board member of a prime American pharmaceutical company stated that “a first-rate academic medical centre in India charges approximately \$1,500 to \$2,000 per case report. That is less than one tenth the cost at a second-tier centre in the United States”.²⁷⁰ More generally, studies show that in the US and the EU the cost of clinical trials is rapidly increasing, by 20% per year, thus rendering off-shoring highly profitable, allowing savings ranging from 50% up to, as reported, 90%.²⁷¹ This enormous cost reduction depends on several elements, especially the lower wages of doctors, nurses, and coordinating investigators, and lower maintenance costs of sites in middle- and low-income countries.²⁷² Secondly, recruitment of patients tends to be much

and the EMA report on off-shored clinical trials.

²⁶⁸ See Levinson D.R., “Challenges to the FDA’s Ability to Monitor and Inspect Foreign Clinical Trials”; EMA report on clinical trials; Glickman et al., “Ethical and Scientific Implications”; Chin R., Bairu M. (eds.), *Global Clinical Trials*; Chin R., Bairu M. (eds.), *Global Clinical Trials Playbook*, Elsevier Academic Press, 2012; Altavilla A., “Ethical Standards for Clinical Trials”; Petryna A., *When Experiments Travel*; Schipper I., Weyzig F., “Ethics for Drug Testing in Low and Middle Income Countries”; Feldschreiber P., *The Law and Regulation of Medicines*; Rowland C., “Clinical Trials Seen Shifting Overseas”, *International Journal of Health Services* 34, 3, 2003; Yee A., “Regulation Failing to Keep up with India’s Trials Boom”, *the Lancet* 379, 9814, 2012.

²⁶⁹ Garnier J.P., “Rebuilding the R&D Engine in Big Pharma”, *Harvard Business Review* 86, 2008, pp. 68-76; Glickman et al., “Ethical and Scientific Implications”, p. 816.

²⁷⁰ Garnier J.P., “Rebuilding the R&D Engine in Big Pharma”, p. 70.

²⁷¹ Wei D., “The How-To of Global Clinical Trials Forecasting, Budgeting and Project Management”, in Chin R., Bairu M. (eds.), *Global Clinical Trials Playbook*, p. 57. The cost saving rate is substantially undisputed and has been confirmed by personal interviews with Merck, Pfizer, Novartis, and GlaxoSmithKline executives.

²⁷² WHO, “Making the most of Existing Health Workers”, in *Working together for Health: the World Health Report*, Geneva, World Health Organization, 2006; and Glickman et al., “Ethical and Scientific Implications of the Globalization of Clinical Research”.

faster in developing countries. Recruitment can be increased by 100%, up to even 500%.²⁷³ Data from the US and the EU suggest that as many as 80% of clinical trials fail to secure enrolment on time, and that this recruitment problem is costly and time-consuming for pharmaceutical companies.²⁷⁴ In this sense, the much higher numbers of potential trial participants and the reduced research costs in, for example, China, India, and South Africa offer considerable opportunities to accelerate recruitment.²⁷⁵ Furthermore, standard testing requires patients to be treatment-naïve.²⁷⁶ For many products representing large market shares in Western countries (such as anti-arthritis or anti-diabetes medications – the recalled Vioxx and Avandia), off-shoring is paramount,²⁷⁷ as virtually no recruitable local patient is treatment-naïve, and none is likely to consent to be treated experimentally given the abundance of valid therapeutic alternatives already on the market.²⁷⁸ Finally, the third strong driver for globalisation of clinical trials is the highly bureaucratic and costly regulatory environment of Western countries. The complexity of regulatory requirements and the significant burdens on clinical investigators to ensure compliance and adequate documentation, while conducting regular training, are strong incentives to move testing sites to countries with younger and more flexible bureaucracies and regulations, where less stringent regulations and/or weaker enforcement can result in faster approval of research protocols.²⁷⁹

We note at this point that the widespread adoption of the ICH Good Clinical

²⁷³ Chin R., “Global Clinical Trials, Study, Design and Planning”, in Chin R., Bairu M. (eds.), *Global Clinical Trials Playbook*, p. 11; and Petryna A., *When Experiments Travel*, chapter I.

²⁷⁴ Altavilla A., “Ethical Standards for Clinical Trials”, p. 67; Annas G.J., “Globalized Clinical Trials and Informed Consent”, *New England Journal of Medicine* 360, 2009; and SOMO, “Briefing Paper: Examples of Unethical Trials”, February 2008, available at <http://www.somo.nl>.

²⁷⁵ Rowland C., “Clinical Trials Seen Shifting Overseas”, p. 555; Glickman et al., “Ethical and Scientific Implications of the Globalization of Clinical Research”, p. 818.

²⁷⁶ That is, not previously exposed to therapeutic equivalents; the issue will be further developed in the forthcoming sections.

²⁷⁷ For this reason, despite the lack of data in public records, it comes as no surprise that EMA and MHRA officials confirmed that both drugs have undergone trials in third countries. The issue of patient naïvety and its link to widespread testing of typical Western diseases in developing countries (in which such products are of very limited use, if any) will be touched upon in the following section.

²⁷⁸ The issue will be further discussed in section 3 *infra*. Here we refer to the rich work of Petryna A., *When Experiments Travel*, with particular attention to the interviews in chapters 1 and 2; see also Rowland C., “Clinical Trials Seen Shifting Overseas”, p. 555.

²⁷⁹ The literature is consistent on the point. We refer to the cited studies in *The Lancet*, *NEJM*, *JAMA*, *BMJ*, and the literature referenced in this section. The point will be further discussed in section 3 and in the next chapter. The relaxation of standards involves mostly the substantive oversight of trial conduct rather than the black letter regulations, which albeit divergent in their wording, are generally informed by the ICH Guidelines.

Practice (GCP) Guidelines can be seen as both an endorsement of and an independent contributor to the globalisation of clinical trials. This will be discussed in the following chapter IV, dedicated to the origin and contents of the rules governing transnational trials.

Consensus as to the existence and magnitude of the clinical trial off-shoring phenomenon is now essentially unanimous, as much in the scientific community as in the minds of the regulatory agencies. What is lacking and, we contend, needed, is a proper analysis of its legal implications. This section laid down the first reason for the necessity of legal reflection upon the uncertainty resulting from the globalisation of clinical trials: the magnitude of the phenomenon. The next section analyses the contentious issues arising in this globalising drive, demonstrating why out-sourcing, while clearly advantageous in economic terms, comes at a cost on the safety and data quality side.

3. Structural biases in data quality and reliability

If the out-sourcing of clinical trials is a widespread and now generally accepted phenomenon, so are the ensuing difficulties. Once again, it is with a certain surprise that one can observe how the topic has received relatively scarce attention in the legal sphere, while persistently raised by both academic and practicing scientists. Even what little legal research there is on the topic seems to not fully appreciate the true nature of the problem, which is substantial rather than merely procedural.²⁸⁰

There is room to argue that the data quality of trial reports off-shored to third countries may be less than optimal, for various reasons. Major concerns comprise (1) structural deficiencies in data control quality, (2) divergences in therapeutic culture, (3) ethical misconduct with scientific implications, and (4) issues related to patient recruitment, treatment-naïvety, and genetic aspects of treatments' success or failure.

(1) The first element to consider is the fact that controlling data flowing from foreign environments is an extremely complex task, requiring resources and infrastructures

²⁸⁰ An example of procedure-focused legal literature on drug safety is Purnhagen K., "The Challenge of Globalization in Pharmaceutical Law: Is an International Approval System Modelled after the European System Worth Considering?", 63 Food and Drug Law Journal, 3, 2008, proposing an international approval system based on the ICH role, without really addressing the substantive issues raised by transnational development and testing. We will discuss those substantive issues now, and the procedural side in depth in chapter IV.

that are difficult to sustain. Regulatory bodies, according to prominent scientific literature²⁸¹ (and in line with the tendency to approach pharmaceutical regulation as a national or regional phenomenon), are very much inwards oriented as they are structured to supervise clinical trial data and pharmaceutical safety in general “in their domestic markets”²⁸² (a design that follows the model adopted and developed in Western markets, as explored in chapter II while discussing the EMA and the FDA). The competent agencies tend therefore to be insufficiently informed on critical elements of clinical research carried out outside their jurisdiction, including the state of the sites, the identity and level of the investigators, the identity and exact background of the trial patients, and therefore the resulting quality of the trial data.²⁸³ The monitoring of clinical trial sites and conduct in third countries is a crucial task for data-receiving agencies, especially the FDA and the EMA for NDAs and MAAs, but one that proves to be arduous if not impossible altogether. It is worth again looking at the numbers retrievable from the FDA and EMA public records. According to the relevant US regulation on the acceptance of foreign data in an NDA,²⁸⁴ site inspection is a key element for the FDA to gain confidence about, or have the ability to validate, the reality and quality of trial data.²⁸⁵ The FDA should be using onsite inspections to ensure that clinical investigators, sponsors, and institutional review boards (IRBs) comply with FDA regulations on good clinical practice while developing and testing investigative drugs. However, although the FDA has unfettered authority to conduct site inspections,²⁸⁶ it is not required to do so. The recalled OIG study report

²⁸¹ See EMA report on foreign clinical trials; Levinson D.R., “Challenges to the FDA’s Ability to Monitor and Inspect Foreign Clinical Trials”; Glickman et al., “Ethical and Scientific Implications of the Globalization of Clinical Research”; Chin R., Bairu M. (eds.), *Global Clinical Trials*; Chin R., Bairu M. (eds.), *Global Clinical Trials Playbook*; Altavilla A., “Ethical Standards for Clinical Trials”; Petryna A., *When Experiments Travel*; Schipper I., Weyzig F., “Ethics for Drug Testing in Low and Middle Income Countries”; Feldschreiber P., *The Law and Regulation of Medicines*; Rowland C., “Clinical Trials Seen Shifting Overseas”; Yee A., “Regulation Failing to Keep up with India’s Trials Boom”.

²⁸² As suggested in Glickman et al., “Ethical and Scientific Implications of the Globalization of Clinical Research”, p. 818.

²⁸³ See Little R.J. et al., “The Prevention and Treatment of Missing Data in Clinical Trials”, *NEJM* 367, 14, 2012, p. 1355; Agrawal V., “International Clinical Trials”, *Bioethics & the Law*, 2012 p. 7; Rowland C., “Clinical Trials Seen Shifting Overseas”; we also refer to the experience reported in section 1 of this chapter when discussing unavailability of data for qualitative research, whereby it was often the case that the agency was not in possession of the relevant data.

²⁸⁴ 21 CFR 314.106: the regulation will be further analysed in chapter IV.

²⁸⁵ This requirement is not exclusive to foreign data, but also applies to US-based trials. Inspection is an essential, although not compulsory, monitoring function for data quality surveillance: CFR 314.100 and following.

²⁸⁶ 21 CFR 314.120(c)(1).

demonstrates that the FDA inspects very few sites either domestically or internationally.²⁸⁷ The FDA itself only inspects 1.2% of domestic (US) trial sites, and in the period between 1998 and 2008, it is reported to have actually inspected less than 1% of non-US sites.²⁸⁸ The EMA report shows slightly different figures, but still extremely low when it comes to the ROW region. The countries with the highest number of inspections are the US (21.9%) followed by Canada (5.7%), India (3.9%), Russia (3.5%), China (1.8%), Philippines (1.8%), South-Africa (1.3%), and Thailand (1.3%), the percentages expressing the rate of inspected trials per total number of registered trials per region.²⁸⁹ It should be of great concern that MAAs and NDAs are generally fleshed with data produced at non-inspected sites. Reliance on local authorities' oversight and enforcement of international standards, the major argument for the 'non-invasive' attitude of Western agencies, should be carefully weighted, as studies also demonstrate a substantial failure to monitor on the side of IRBs. While data on ROW regions are extremely difficult to retrieve, one study showed that about 56% of 670 researchers surveyed from ROW regions confirmed that the research they undertook was actually revised by the competent IRB or the local health ministry.²⁹⁰ It is also worth recalling at this point that, as suggested above, the ROW regions have the highest rate of patients per site. There seems to be here a form of asymmetry between the formal powers attributed to the regulators, and the practical ability of said regulators to effectively exercise such powers.

(2) The second element to consider is very much tied to the first, and relates to what we have described as 'therapeutic culture'.²⁹¹ This concept is used to synthetically describe the multilateral relationship between patients, doctors, medicine producers and providers, and the monitoring authorities. Such relationship can vary considerably from country to country, and finds reflection in regulatory requirements. Mostly, as regards

²⁸⁷ Domestically, inspections are not so much necessary for the control of regular clinical practice, but called for in cases of malpractice or regulatory infringement. The absence of clear registers on the totality of clinical trials taking place at a given time is also a factor.

²⁸⁸ While it is difficult to break down the number between regions, the variation is between 0.5% and 1.4%, see Levinson D.R., "Challenges to the FDA's Ability to Monitor and Inspect Foreign Clinical Trials", p. 5.

²⁸⁹ EMA report on foreign clinical trials, p. 27.

²⁹⁰ Hyder A.A., et al., "Ethical Review of Research: a Perspective from Developing Country Researchers", *Journal of Medical Ethics* 30, 2004, pp. 68-72; the equivalent numbers in the US and EU areas are close to 100%.

²⁹¹ See the brief presentation of the concept offered in chapter I: the idea is taken from Daemrich A., *Pharmacopolitics – Drug Regulation in the United States and Germany*, The University of North Carolina Press, 2004, pp. 243-48.

clinical testing practices, the differences are measurable in terms of greater or lesser risk aversion for developed countries,²⁹² and greater or lesser involvement of the patient in therapeutic decisions when it comes to developing countries.²⁹³ To give a practical example of both scenarios, let us consider the WHO Declaration of Helsinki of 2008 on ethical guidelines for research involving human subjects.²⁹⁴ The Declaration sets the desirable standard that every patient enrolled in a clinical trial should be guaranteed access to the best recognised treatment identified for the health condition at stake. While the EMA has developed guidelines for the application of this criterion, the FDA, in complete disregard of the Declaration, requires in the overwhelming majority of trial studies the traditional test against placebo.²⁹⁵ This situation is possibly in the process of changing, as the US Supreme Court recently ruled that the ethical guidelines of the Helsinki Declaration are rapidly attaining the status of international human rights law.²⁹⁶ But until recently, when questioned on the subject, FDA officials respond that the placebo versus best proven therapy issue is “a mere ethical concern, and not a regulatory one”.²⁹⁷ The contrast with the responses of EMA officials to the same question is sharp, as they appear strict in elevating the rule to a “stringent requirement for the validity of a study trial”.²⁹⁸ Where there is a risk to the patient’s health, the therapeutic culture of the EU takes what can be considered as a conservative or ‘patient comes first’ approach, whereas the US sticks to the placebo rule, considering it the only valid option for proper test results. This is not without consequences, as the two tests are not only liable to present diverging results, but, as senior medical assessors from both the EMA and the FDA agree, “they simply constitute

²⁹² *Ibidem*: in this analysis, Daemrich refers to the work of Hofstede G., *Culture's Consequences: Comparing Values, Behaviors, Institutions and Organizations across Nations*, Sage, 2001, and in particular to the use of indices to measure several cultural variables, including for the purposes of this study “uncertainty avoidance” and “individualism/collectivism”.

²⁹³ *Ibidem*: the relevant index is in this case the “power distance”, measuring the ability of a society to handle inequalities, specifically here inequalities in education and overall access to information for informed consent. This will be further discussed below.

²⁹⁴ WHO, *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Declaration of Helsinki, 2008, CIOMS, Ethical Guidelines n.10.

²⁹⁵ Bairu M., “Bioethical Consideration in Global Clinical Trials”, in Chin R., Bairu M. (eds.), *Global Clinical Trials*, pp. 21-29. See FDA regulations 21 CFR 314.126.

²⁹⁶ *Pfizer Inc. v. Rabi Abdullahi et al.*, US Supreme Court 130 S. Ct. 534, 2010.

²⁹⁷ Personal interview with former FDA senior medical assessor Dr. Jur Strobos, 12 March 2012.

²⁹⁸ Personal interview with senior medical assessor at the MHRA and EMA consultant Dr. Peter Feldschreiber, 27 February 2011. It has to be noted though, that as strong as such a statement is in principle, given the limited inspection and monitoring activity of the EMA in off-shore trials, the effects are hardly measurable.

different types of tests, and mixing the two is scientifically questionable to say the least”.²⁹⁹

On the other hand, when it comes to developing countries, the most contentious issue is informed consent.³⁰⁰ This topic is as much an issue of therapeutic culture as it is one of ethical misconduct, and necessitates a separate discussion.

(3) Ethical concerns as regards out-sourced clinical trials are many-fold. To link the discussion with the previous paragraph, the first element to be discussed is informed consent. Lack of voluntary and adequately informed consent to clinical trials in developing countries is unfortunately extremely common.³⁰¹ The aforementioned lack of IRB supervision opens the door to trials of experimental medicines the safety of which, for testing in humans, has not yet been established. A study on clinical trials conducted in China in 2004 demonstrates that 90% of published clinical trials were not corroborated by ethical review of the relevant protocols, and only 18% reported an adequate discussion on informed consent with participants.³⁰² A 2008 SOMO study reports similar data, not on a country but on a product basis, demonstrating the lack of voluntary informed consent of patients involved in clinical trials conducted in several ROW countries.³⁰³ Finally, the recent US Supreme Court judgment in *Pfizer*,³⁰⁴ adverted to above, was a response to a ground-breaking lawsuit based on ethical misconduct in Nigeria, where an experimental drug for meningitis was given to child patients without informing the patients and their families of the existence of an alternative and proven treatment.³⁰⁵ It is interesting to note that the defence in that case argued that no international norm existed requiring physicians to obtain informed consent for the use of experimental drugs.³⁰⁶

²⁹⁹ The quote is from the interview with MHRA Dr. Feldschreiber, however the FDA’s Dr. Strobos agreed on the substance: “scientifically these are hardly comparable methods”.

³⁰⁰ Daemrich A., *Pharmacopolitics*, referring to Hofstede G., *Culture’s Consequences*, in pointing out how this issue falls within the scope of both “power distance” and “individualism/collectivism”.

³⁰¹ Altavilla A., “Ethical Standards for Clinical Trials”, p. 69; Bairu M., “Bioethical Consideration in Global Clinical Trials”, in Chin R., Bairu M. (eds.), *Global Clinical Trials*, pp. 21-29.

³⁰² Zhang D. et al., “An assessment of the Quality of Randomized Controlled Trials Conducted in China”, *Trials*, 9, 2008, p. 22.

³⁰³ Schipper I., Weyzig F., “Ethics for Drug Testing in Low and Middle Income Countries”, pp. 27-64, reporting the lack of informed consent and ethical reviews on trials for *Abilify*, *Olmeted*, and *Seroquel*.

³⁰⁴ *Pfizer Inc. v. Rabi Abdullahi et al.*, US Supreme Court 130 S. Ct. 534, 2010.

³⁰⁵ The experimental drug was the antibiotic Trovan (later pulled out of the market): patients and their families were not informed of the possibility of treatment via Rocephin, a low-dosage FDA-approved antibiotic.

³⁰⁶ A technically true statement, which may account for the Supreme Court’s attempt to elevate the Declaration of Helsinki to the status of international human rights law.

A different type of problem is represented by discrepancies between desired results and the actual effects of trials on local public healthcare. According to the Helsinki Declaration, clinical trials should be tailored to the health conditions and needs of the local populations.³⁰⁷ However, studies have reported that the overwhelming majority of medicines tested in developing countries target diseases that are typical of Western developed countries,³⁰⁸ and rarely address local health issues.³⁰⁹ A further and related concern is that of double standards. In export-oriented countries, such as India, studies have demonstrated that export products are subject to greater regulatory oversight than those destined for local use, thus neglecting if not aggravating local medical needs.³¹⁰ One of the very few ‘third-world diseases’ for which in-depth research has been financed and treatments successfully developed is HIV, which has a very specific history of its own, and which has been affecting Western countries deeply for over two decades.³¹¹

(4) A further reason to question the quality of the data arising from off-shore clinical trials concerns patient recruitment criteria and, on a related note, the genetic diversity of patient populations in diverse regions of the world. The problem can be summarised as follows. Testing protocols for new medicines require the patient population of the trial to be treatment-naïve.³¹² This implies that patients involved in clinical trials must not have been exposed to therapeutic equivalents before undergoing the trial.³¹³ Such

³⁰⁷ WHO, *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Declaration of Helsinki, 2008, CIOMS.

³⁰⁸ Glickman et al., “Ethical and Scientific Implications of the Globalization of Clinical Trials”, reporting the overview of “Global Pharmaceutical Sales by Region” carried out by Health IMS, 2009.

³⁰⁹ Treatment of local diseases is extremely difficult to incentivise. While about 80% of pharmaceutical consumption takes place in the EU and the US, profitability is linked to sales in such markets. Diseases such as tuberculosis, which seriously affect several ROW countries, only get covered insofar as public incentives are in place.

³¹⁰ Berman A., “The Role of Domestic Administrative Law in the Accountability of IN-LAW: The Case of ICH”, in Pauwelyn J., Wessel R.A., Wouters J. (eds.), *Informal International Lawmaking*, Oxford University Press, 2012, pp. 468-499.

³¹¹ The history of HIV has produced an immense body of literature, an account of which is beyond the scope of this work. It is however worth recalling that this is an example of public expenditure for medical research with the aim of overcoming the lack of profitability of private R&D for HIV treatments. The incredible advances that have been made in the field are largely attributable to the PEPFAR/Emergency Plan, the President’s Emergency Plan for AIDS Relief, created by US President George W. Bush to fight the global AIDS/HIV pandemic. That plan committed \$15 billion over the period 2003-2008.

³¹² ICH Guideline E10, *Choice of Control Group and Related Issues in Clinical Trials*, adopted by EMA CPMP, July 2000, issued as CPMP/ICH/364/96, and FDA regulation published in the Federal Register, 14 May 2001, Vol. 66, No. 93, pp. 24390-24391.

³¹³ A fact *per se* scientifically contentious, as study results on a naïve patient are likely to differ from those on a patient previously exposed to alternative treatments (and the target population is often composed of the latter kind of patients): see Bairu M., “Bioethical Consideration in Global Clinical

a requirement is at odds with the widely accepted phenomenon that a vast majority of clinical tests are conducted for widespread ‘developed-country diseases’, for which alternatives may have been on the market for decades.³¹⁴ This has two related consequences. First, the pool of potential trial participants is extremely limited in developed countries, and secondly, the number is even more dramatically reduced by the existence of proven and marketed alternatives.³¹⁵ This is *per se* problematic: because of the requirement of naïvety, no trial is conducted in comparison with existing treatments on the target population’s market. For common diseases such as arthritis (the condition Vioxx was designed to treat), there is simply no evidence of comparative trials among the numerous marketed medicines available.³¹⁶ The need to recruit treatment-naïve patients is a strong driver of globalisation, as recalled earlier: the inevitable ensuing issue is that the trial population differs substantially from the target population. Geographically distinct groups are characterised by differences in genetic profiles that, as studies have demonstrated, affect the safety and effectiveness of medicines.³¹⁷ The consequent question is whether the ‘social ecology’ and genetics of a study population are transferable to the target population for marketing and consumption of a particular medicine (where effective alternative therapies are usually already available).³¹⁸ The scientific community is fiercely divided on the topic. Clearly, scarce access to clinical data, described in section 1 of this chapter, does not help the quest for a conclusive answer, leaving uncertainty as the winner of the contest.

Trials”, in Chin R., Bairu M. (eds.), *Global Clinical Trials*, pp. 21-29; Cohen-Kohler J.C., Esmail L.C., “Scientific Misconduct, the Pharmaceutical Industry and the Tragedy of Institutions”, *Medicine and Law* 26, 2007, pp. 431-446.

³¹⁴ The issue is thoroughly examined by Petryna A., *When Experiments Travel*, in chapter 1, where she crafts the effective term “treatment saturation”.

³¹⁵ Petryna A., *ibidem*, p. 124.

³¹⁶ This conclusion is the result of cross-referencing available clinical trial registers for NDAs and MAAs in the US and the EU. Due to the partiality of such data, the question was raised directly with EMA and FDA medical assessors. Confirmation came from both agencies.

³¹⁷ Glickman reports that “a study of 42 genetic variants associated with pharmacologic response in drug studies showed that more than two thirds had significant differences in frequency between persons of African ancestry and those of European ancestry”: Glickman et al., “Ethical and Scientific Implications of the Globalization of Clinical Trials”, p. 819. See also Goldstein D.B., Tate S.K., Sisodia S.M., “Pharmacogenetics Goes Genomic”, *Nature Reviews Genetics* 5, 2004, p. 76.

³¹⁸ Altavilla A., “Ethical Standards for Clinical Trials”, p. 69; Glickman et al., “Ethical and Scientific Implications of the Globalization of Clinical Trials”, p. 819.

4. Is uncertainty the conclusion?

Drafting this chapter has been a challenging exercise. The practical impossibility of carrying out qualitative case studies represented, and in a way still represents, a serious obstacle to the achievement of this chapter's goal: the grounded analysis of the provenance, quality, and compatibility of scientific data from off-shore sources. Facing such difficulties, the structure has been reshaped, following what we have defined as a 'second-best' option. This scheme has a number of shortcomings in terms of consistency and solidity of the data. First, the picture shifts from specific to general, and second, even in the general analysis the sources and data are rather fragmented, making it hard to reach positive conclusions. It has however been possible to raise several concrete issues within the sections of this chapter, and it is now time to draw the threads together.

The first point is the existing consensus within prominent scientific literature as to serious problems regarding the general reliability of data from developing countries. We have broken down the issue into four sub-aspects: (1) structural deficiencies in data control quality, (2) divergences in therapeutic culture, (3) ethical misconduct with scientific implications, and (4) issues related to patient recruitment, treatment-naïvety, and genetic aspects of treatments' success or failure. Of these aspects, numbers (1), (3), and (4) (as regards treatment-naïvety issues) are basically non-contentious. The scientific community and regulators from both the EMA and the FDA concur in identifying structural deficiencies in data quality due to lack of monitoring, inexperience of local investigators, relaxed regulatory requirements in terms of compliance with basic ethical standards, and fundamental uncertainties regarding the exact nature of trials at off-shore sites. The idea of diverging 'therapeutic culture' sustains this idea via a different perspective. There is not simply a lack of monitoring or inexperience. In the framework of regulations unavoidably designed in a fashion that leaves an ample margin of appreciation for the investigator to evaluate the data, different cultural imprintings as to how therapy is conducted exert significant influence on the gathering and interpretation of said data. To what extent this factor is taken into account when data are shipped to a different cultural environment (or to use the terminology of this study, the receiving market) is difficult to measure, but the issue is real.³¹⁹ Also real is the problematic use of treatment-naïve patients, for the array of

³¹⁹ In a personal interview, a senior medical assessor of the EMA, when queried on the subject, responded: "Yes, this is an issue that we have troubles measuring, and procedural requirements can

reasons suggested above, ranging from the uselessness of most experimental treatments to the trial population, to differences in both therapeutic experience and genetic patterns between trial and target populations. It has also been shown that off-shoring of clinical trials is an increasingly widespread phenomenon, with an exponential growth rate over the last two decades which is unlikely to stop, thus rendering issues of data quality more and more salient.

It is in this context that we need to consider the impossibility of undertaking a full, in-depth, product-specific analysis. We closed the first section of this chapter with a claim that such impossibility could *per se* indicate issues with substantial regulatory compliance. In light of the analysis carried out in the subsequent sections, we suggest that since consensus on the phenomenon of out-sourcing trials is essentially complete, and consensus on the ambiguity of the quality of the resulting scientific data is, if not complete, sufficiently broad to seriously question said quality, a concrete legal issue ensues regarding substantial compliance with requirements of safety and efficacy in the receiving markets. The uncertainty surrounding the life cycle of specific products (and especially, as suggested here, the location of testing sites), if frustrating in terms of reaching certain research conclusions, leaves the door wide open to such a claim. Whereas a measure of scientific uncertainty is unavoidable as regards the safety and efficacy of any new treatment, here the situation seems to be more complex. The complicating factors impacting the quality of the assessment exhibit traits that arise from the regulatory process (or rather its limitations) rather than the products themselves. This poses a legal problem (a form of legal uncertainty), and should be addressed accordingly. Chapter VII will provide an analysis mirroring the one offered in this chapter, through the lens of the judiciary, in an attempt to explore the potential for courts to improve scientific data quality through discovery and disclosure mechanisms.

only do so much to overcome it. We work on the assumption that when GCP guidelines are in place the data is robust, but we have scarce information on *how* the implementation is carried out.”

CHAPTER IV

QUESTIONING THE INSTITUTIONAL DESIGN 2

ORIGIN AND CONTENT OF THE RULES: (NON-?)INCLUSIVENESS OF PROCEDURES

This chapter takes over the questioning of the institutional design and shifts the focus to a different and equally crucial aspect of the regulatory intricacies of pharmaceutical pre-marketing procedures. Issues previously raised in terms of effectiveness will now be investigated in light of their impact on the accountability and legitimacy of the legal frameworks in which they materialise. First the analysis describes the legal basis on which pre-marketing assessments in the US and EU domestic frameworks are permeated by exogenous elements. Secondly, the discussion will shift to the theoretical justifications for the progressive abandonment of traditional democratic legitimacy in the rule-making mechanisms for the pharmaceutical sector.

1. The regulatory requirements for accepting foreign clinical data in EU/US markets

Chapter III illustrated how, for a now considerable period of time, the FDA and the EMA have accepted data resulting from clinical studies conducted in third countries in support of safety and efficacy claims in NDAs and MAAs.³²⁰ This section reviews the relevant FDA and EMA regulations for foreign data acceptance with a view to accounting for the rules governing this phenomenon.

Under section 21 CFR 312.120(c)(1), the FDA used to accept foreign clinical trial data with the stringent requirement that the trial conformed with the option providing

³²⁰ See sections 2 and 3 of chapter III, and also *infra*.

“greater protection of the human subjects”,³²¹ as between the ethical principles and related recommendations as provided by the Helsinki Declaration,³²² or the “laws and regulations of the country in which the research was conducted”.³²³ This alternative choice suggested a conception of the Helsinki provisions as minimum standards to be met or surpassed by national regulatory requirements.

However, in April 2008, the FDA published a regulatory change, removing the requirement for clinical trials conducted in non-US countries to comply with the Helsinki Declaration³²⁴ in its original version of 1989. This change provides, under 21 CFR 312, that the FDA will accept foreign clinical trials conducted in accordance with the Good Clinical Practice (GCP) regulations³²⁵ as developed through ICH procedure, namely Guideline E6.³²⁶

This raised significant alarm as regards a series of essential Helsinki Declaration requirements, in particular those regarding the safeguarding of vulnerable subjects as regards the potential dangers of the use of placebo (in terms of lost opportunities to undergo an existing treatment).³²⁷ Concerns raised by the abandonment of the Helsinki

³²¹ Wilson J.B, Gomez-Panzani E., “United States Regulations”, in Chin R., Bairu M. (eds.), *Global Clinical Trials – Effective Implementation and Management*, Elsevier Academic Press, 2011, p. 43.

³²² In its version of 1989, WHO, *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Declaration of Helsinki, 1989, CIOMS. It is worth noting that at the time, the debate over placebo versus proven alternative therapy was not as developed as it became in the following decade. That delay is reflected in the contents of the 1989 version of the declaration.

³²³ Wilson J.B, Gomez-Panzani E., “United States Regulations”, in Chin R., Bairu M. (eds.), *Global Clinical Trials*, p. 45.

³²⁴ *Ibidem*, p. 43; see the decision at Federal Register. 2008 Apr 28; 73(82): 22800–22816.

³²⁵ The amended version of 21 CFR 312.120 as revised in October 27, 2008 provides that foreign data can be accepted when: “(i) The study was conducted in accordance with good clinical practice (GCP). For the purposes of this section, GCP is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected. GCP includes review and approval (or provision of a favourable opinion) by an independent ethics committee (IEC) before initiating a study, continuing review of an ongoing study by an IEC, and obtaining and documenting the freely given informed consent of the subject (or a subject's legally authorized representative, if the subject is unable to provide informed consent) before initiating a study. GCP does not require informed consent in life-threatening situations when the IEC reviewing the study finds, before initiation of the study, that informed consent is not feasible and either that the conditions present are consistent with those described in 50.23 or 50.24(a) of this chapter, or that the measures described in the study protocol or elsewhere will protect the rights, safety, and well-being of subjects; and (ii) FDA is able to validate the data from the study through an onsite inspection if the agency deems it necessary.”

³²⁶ ICH, *Tripartite Harmonised Guidelines – Guideline for Good Clinical Practice E6* (R1, 10 June 1996), available at <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>.

³²⁷ With the caveat mentioned above, on the subsequent development of the placebo versus most advanced treatment alternative debate. See Wilson J.B, Gomez-Panzani E., “United States

Declaration were addressed by the FDA's inclusion in the GCP requirements of "review and approval (or provision of a favourable opinion) by an independent ethics committee (IEC) before initiating a study, continuing review of an ongoing study by an IEC, and obtaining and documenting the freely given informed consent of the subject".³²⁸ It is noteworthy that the text of the US provision explicitly refers to "standard[s] for the *design, conduct, performance, monitoring, auditing, recording, analysis, and reporting* of clinical trials" (emphasis added), which are strong procedural requirements in accordance with ICH Guideline E6. Despite its ostensibly substantive content, this set of rules falls short of effectively addressing the critical issues previously identified (such as for example the issue of patient-naïvety, or the inability to solve the placebo versus best available alternative as a regulatory or ethical question). This is a significant *aperçu* of the phenomenon described in this work as a dichotomy between national frameworks and transnational practices. The strong internal regulatory regime in place in the US (see *supra* chapter II) is open to exogenous elements (foreign data) which are assessed on the basis of standards strongly designed from a procedural perspective but rather generic on substance, and principally through the possibility for the FDA to conduct onsite inspections (in practice a very limited activity, see again *supra* chapter III).

We have posited that the out-sourcing phenomenon for clinical trials is characterising modern practice in the EU as much as in the US. The EMA, up until 2014, required that clinical trials included in MAAs be conducted in accordance both with GCP,³²⁹ and with the ethical standards of Directive 2001/20/EC.³³⁰ The EU Directive has been implemented in all 28 Member States, and three EEA countries (Norway, Iceland and Lichtenstein) comply with the relevant requirements as well.³³¹ EU Directive 2001/20/EC used to apply to all clinical trials on investigative medicinal products, from Phase II to Phase IV (pharmacovigilance). A follow-up was achieved with Directive 2005/28/EC, approved in April 2005, incorporating the Good Manufacturing Practice rules into the

Regulations", in Chin R., Bairu M. (eds.), *Global Clinical Trials*.

³²⁸ 21 CFR 312.120 (i).

³²⁹ See Directive 2001/83/EC, Annex I, as amended by Directive 2003/63/EC.

³³⁰ Directive 2001/20/EC of the European Parliament and of the Council, 4 April 2001, On the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

³³¹ Wilson J.B., "European Union Regulations", in Chin R., Bairu M. (eds.), *Global Clinical Trials*, p. 55.

overall GCP scheme.³³² The EU regulations did not differentiate at a legislative level between the requirements for clinical trials conducted within the EU territory and those carried out in third countries.³³³ Again, however, the major tool for quality monitoring is provided by the power of inspection of clinical trials sites.³³⁴

As mentioned in chapter III, a significant reform of EU pharmaceutical regulation was recently approved, with the adoption of a new Regulation on clinical trials. With its current proposal, the Commission seeks to modernise the legal framework of clinical trials by addressing a series of shortcomings ascribed to the regime governed by Directive 2001/20/EC. The proposal seems to go in the direction of abolishing differentiations in practice between trials held in the Union and in third countries (that is, towards the elimination of a ‘special’ status for the latter).³³⁵ For the purpose of this chapter, it is worth noting the provisions of chapter 8 of the Regulation,³³⁶ on the conduct of trials. The intended effect of the articles contained in this chapter is to draw together the rules introduced by Directive 2005/28/EC, laying down principles and guidelines on good clinical practice, and the Commission guidance documents on the topic. Rather than detailing principles and guidelines for actual trial conduct, however, the proposal cross-refers explicitly to ICH Guidelines on the matter (specifically ICH Guideline E6), and in substance focuses on a series of provisions on monitoring of trial sites, adequacy of trial population, and duties (articles 47–59), *de facto* acknowledging an established trend that favours policy documents *vis à vis* hard law instruments in governing such highly technical (and therefore constantly evolving) issues. The key factor, for all intents and purposes, remains the inspection mechanism, with all the limits underlined *supra*.

The basic set of rules justifying and allowing the reported significant use of

³³² Commission Directive 2005/28/EC of 8 April 2005, laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products.

³³³ In the wording of both Directives 2001/20 and 2005/28, the requirements for the validity of trials submitted for MAAs apply indistinctly to data from MSs and third countries. Unlike the US provisions, the EU does not specify distinct requirements for acceptance of foreign data.

³³⁴ Regulation (EU) No 536/2014 of the European Parliament and of the Council on clinical trials for medicinal products for human use and repealing Directive 2001/20, OJ L 158, 2014, art 78; Directive 2005/28/EC, arts. 21–30.

³³⁵ *Ibidem*, Recital 65: “The Commission should be able to control whether Member States correctly supervise compliance with this Regulation. Moreover, the Commission should be able to control whether regulatory systems of third countries ensure compliance with the specific provisions of this Regulation and Directive 2001/83/EC concerning clinical trials conducted in third countries.”

³³⁶ *Ibidem*, chapter 8 on the conduct of a clinical trial, supervision by the sponsor, training and experience, and auxiliary medicinal products.

foreign data in both the US and EU markets is therefore grounded in the aforementioned ICH Guideline E6 on GCP (discussed in detail in the next section). The basis for foreign trial acceptance is thus quite similar, with both sets of rules largely comprising ‘soft’ procedural requirements developed transnationally at ICH level (and subsequently transposed into domestic governance through soft instruments such as policy documents – see the next section).

Such an approach is, as suggested, intrinsically procedural, falling short of properly addressing the series of substantial concerns that were raised in the previous chapter.³³⁷ Moreover, the only real option for the FDA and the EMA to supervise the fulfilment of GCP requirements would be to enforce their monitoring and inspection powers. As already suggested, such enforcement activity has proved very limited in practice and can only provide extremely narrow coverage of the overall transnational clinical testing scenario.³³⁸

It is worth briefly recalling the findings of recent studies on the use of foreign data by the EMA and the FDA. According to the aforementioned OIG report:³³⁹

- 80% of approved NDAs in 2008 contained data from foreign clinical trials. A majority of both trial population and trial sites were located in non-US countries.
- The FDA reported inspections in just under 1% of sites located outside the US.
- The report concludes that challenges to conducting inspections in third countries sites and limited availability of resulting data (similar to the ones this research has encountered) “inhibit the FDA’s ability to monitor foreign clinical trials”.

The report conducted on the issue of foreign clinical trials submitted to the EMA in MAAs suggested similar difficulties in managing the flow of foreign data, and serious

³³⁷ In particular, monitoring of data quality, the implementation of procedures conflicting with diverse therapeutic cultures, and patient-naïvety issues.

³³⁸ See section 3 of chapter III on inspections and related challenges.

³³⁹ See Levinson D.R., “Challenges to the FDA’s Ability to Monitor and Inspect Foreign Clinical Trials”, DHHS - OIG, 2010, and section 2 of chapter III.

limitations upon the agency's ability to conduct inspections.³⁴⁰ In an attempt to overcome such structural obstacles, and in order to foster closer cooperation on the off-shoring of clinical trials, the EMA and the FDA have launched a joint initiative to collaborate on GCP for international inspections. The initiative identifies a series of key objectives:³⁴¹

- To conduct periodic information exchanges on GCP-related information in order to streamline sharing of GCP inspection planning information, and to communicate effectively and in a timely manner on inspection outcomes.
- To conduct collaborative GCP inspections by sharing information, experience and inspection procedures, cooperating in the conduct of inspections and sharing best-practice knowledge.
- To share information on interpretation of GCP, by keeping each regulatory agency informed of GCP-related legislation, regulatory guidance and related documents, and to identify and act together to benefit the clinical research process.

The initiative is the first official document recognising the necessity of cooperation not only in the rule-making side of pharmaceutical safety, but also, and essentially, in the conduct of the trials. The attempt to overcome disparities in GCP interpretation is a key and welcome element of this policy document. However, its ability to practically impact the state of affairs in the US and the EU is intimately linked to its enforceability, on the one hand, and its financing on the other. The original idea was to have an 18-month pilot period, starting in September 2009. As of today,³⁴² the initiative has produced limited results, the main one being a further confirmation of the difficulties encountered by the agencies in performing statistically significant inspections.³⁴³

³⁴⁰ See EMA, *Clinical Trials Submitted in Marketing Authorization Applications to EMA: Overview of Patients recruitment and the Geographical Location of Investigator Site*, Doc. Ref. EMA/INS/GCP/154352/2010, 5 November 2010, and EMA/INS/GCP/676319/2012, 11 December 2013; see also section 2 of chapter III.

³⁴¹ See “EMA-FDA GCP Initiative -Terms of engagement and procedures for participating authorities”, EMA Doc.Ref. EMEA/INS/GCP/538414/2008 FDA Mod. of 20 August 2009.

³⁴² March 2015. In the fall of 2013, a new joint initiative was launched based on the claimed positive outcomes of the 2009 experience. There is an expectation that this report will provide statistically more relevant data on inspections in third countries.

³⁴³ See EMA and FDA, ‘Report on the Pilot EMA-FDA GCP Initiative’, Doc. Ref. EXT/INS/GCP/56289/2011, at 13, Table 1.

2. The GCP and SPCT Guidelines – Essential examples of harmonisation through ICH

The previous section has shown that the essential element of foreign clinical trial acceptance in both the EU and the US is the fulfilment of the requirements laid down in ICH Guideline E6 on Good Clinical Practice (GCP). In the words of the ICH Steering Committee:³⁴⁴

The tripartite harmonised ICH Guideline was finalised under *Step 4* in May 1996. This Good Clinical Practices document describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and IRBs. GCPs cover aspects of monitoring, reporting and archiving of clinical trials and incorporating addenda on the Essential Documents and on the Investigator's Brochure which had been agreed earlier through the ICH process.

A second essential tool in the transnational regulatory process leading to marketing approval of new products is found in ICH Guideline E9 on Statistical Principles on Clinical Trials (SPCT). As acknowledged by the document itself:³⁴⁵

The focus of this guidance is on statistical principles. It does not address the use of specific statistical procedures or methods. Specific procedural steps to ensure that principles are implemented properly are the responsibility of the sponsor. Integration of data across clinical trials is discussed, but is not a primary focus of this guidance.

In describing such responsibility, the documents set a series of procedural standards ranging from the institution of a review ethics committee to the obligations of investigators towards the patients, the method of double-blind randomisation,³⁴⁶ and stress the obligations of sponsors in trial management. These are very complex documents, technically and procedurally specific, that however provide no firm guidance on the interpretation of data and risk-benefit parameters.³⁴⁷ On the substance of data

³⁴⁴ ICH, *Tripartite Harmonised Guidelines – Guideline for Good Clinical Practice E6* (R1, 10 June 1996), available at <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>.

³⁴⁵ ICH, *Tripartite Harmonised Guidelines – Statistical Principles for Clinical Trials E9* (1998), available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf, p. 2.

³⁴⁶ The double-blind randomised test requires patients to be equally randomly distributed between those receiving the experimental treatment and those receiving placebo. Investigators shall be equally distributed in the same fashion. Both groups ignore who is receiving what.

³⁴⁷ The guidelines are deferential to the autonomy of investigators in these matters. It is interesting to note how in other fields, the idea of risk assessment is narrowly defined instead of broadly

interpretation, the terrain where experience, funding and therapeutic cultures play crucial roles,³⁴⁸ investigators enjoy a very wide margin of appreciation.

It is interesting for the purposes of our study to focus on the mechanisms of production of guidelines such as ICH E6 (GCP) and E9 (SPCT), for a further discussion on the (non-)inclusiveness of their adoption procedures. Arguably, over and beyond simple sets of minimum technical standards, these rules represent the expression of a mercantile attitude, where rapid access to market and free flow of products are the fundamental policy choices. The complicating factors previously described make room for the hypothesis that these choices are transnationally more achievable than the parallel commitments to health protection³⁴⁹ – although to what extent exactly we cannot say, due to the impossibility of conducting in-depth case studies. Nevertheless the observations made in chapter II suggest that the hypothesis should not be dismissed hastily. For instance the discussed criteria for selection of trial populations, frequent disregard for local health concerns, and divergences between trial and target populations are contentious issues both from a scientific and policy perspective.³⁵⁰ Moreover, the analysis in this chapter suggests that an argument can be made pertaining to the mechanisms of drafting and adoption of ICH documents, to the effect that rule-making mechanisms suffer from a lack of transparency and openness that moves the debate beyond the substance of the rules and embraces their legitimacy and the accountability of the leading agents. The key question being, “who makes the fundamental value choices?”

We have already outlined the structure of the ICH, which consists basically of representatives of the EU, Japan, and US regulatory authorities and regional representatives of the pharmaceutical industry,³⁵¹ and which focuses on the harmonisation

suggested, such as in the case of nuclear and radioactive materials, where the risk/benefit assessment is stroked down through a precise equation: see Council Directive 2013/59/EURATOM laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, OJ 2014, L13/1, and EU Commission Final Report “Assessment of the Consequences of the Presence of Toxic Elements in some Common Radioactive Waste Streams”, available at <http://ec.europa.eu/energy/nuclear/studies/doc/other/eur18211.pdf>, p. 137 ff.

³⁴⁸ We refer back to the analysis in section 3 of chapter III.

³⁴⁹ See the ‘ICH Vision’ section on the ICH website, www.ich.org.

³⁵⁰ See section 3 of chapter III.

³⁵¹ The EMA (together with a representative from the Commission), the FDA, Japan Ministry of Health, European Federation of Pharmaceutical Industries and Associations (EFPIA), JPMA (Japan Pharmaceutical Manufacturers Association), and PhRMA (Pharmaceutical Research and Manufacturers of America). See Arnold R. B., *Annex 1 Co-Sponsors of the Conference*, in D’Arcy P.F., Harron D.W.G. (eds.), *Proceedings of the First International Conference on Harmonization*

of technical requirements for drug approval. This section describes its actual functioning.³⁵² It will be recalled that in addition to the six original members, four ‘observers’ participate in the ICH.³⁵³ The role of this group of non-voting members is to foster communication between countries that are not organised through the ICH and those that are. The observers are the World Health Organisation (WHO – which plays a strong role in connecting ICH and non-ICH countries for the purpose of ensuring comparable minimum standards, circulating ICH Guideline drafts around non-ICH – especially developing – countries for comment and criticism), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), and Health Canada (the Canadian regulatory authority for food and drug safety).

In the early stages of its existence, the ICH emphasised the need for cooperation between the major players in the pharmaceutical market. It was intended to serve as a platform for experts in the pharmaceutical industry from the three key regions – the US, the EU, and Japan – to discuss technical and scientific aspects of pharmaceutical authorisation requirements, with the principal goal of lessening the number of trials required to be carried out for research and development of new treatments. This was sought to be achieved through harmonisation of the interpretation and design of technical guidelines for the pharmaceutical authorisation process, including marketing approval reviews. The decision-making process for the adoption of technical guidelines is, accordingly, based on negotiation among the members from the regulatory bodies and the pharmaceutical industry.

As previously stated, the main ICH decision-making body is the Steering Committee (SC), which can unanimously issue guidelines for its members.³⁵⁴ The SC is supported by ICH Coordinators and the ICH Secretariat. As the main working unit of the ICH, the SC not only determines procedures and policies for the ICH and selects topics for harmonisation, but also monitors the progress of all harmonisation activities. The SC

Brussels 1991 xxi, xxi-xxiii.

³⁵² The reconstruction that follows is based on the data retrievable from the ICH website, www.ich.org, but is also based on (and owes much to) the work of Berman A., “Informal International Law Making in Medical Products Regulation”, in *Informal International Law Making – Case Studies*, TOAEP, 2012 and Purnhagen K., “The Challenge of Globalization in Pharmaceutical Law: Is an International Approval System Modeled after the European System Worth Considering?”, 63 Food and Drug Law Journal, 3, 2008, pp. 623-645.

³⁵³ Follow the ‘Organisation of ICH’ hyperlink from the ‘About ICH’ section on the ICH website.

³⁵⁴ Follow the ‘Organisation of ICH’ hyperlink from the ‘About ICH’ section on the ICH website.

consists of fifteen members (representing the six voting members plus the observers described above).³⁵⁵ The pharmaceutical industry is thus represented not only regionally but also through its international representative body, IFPMA. The influence of the pharmaceutical industry is extraordinary if we take a closer look at the organisation of the ICH Secretariat. The purpose of the Secretariat is, generally speaking, administrative support for the SC with research and documentation.³⁵⁶ Additionally it coordinates working and discussion group meetings. This body operates directly from the IFPMA office in Geneva.

Generally, harmonisation activities of the ICH fall into four categories, each of which has a different procedure. The procedures consist of the development of a new guideline (Formal ICH Procedure), the creation of questions and answers to assist the implementation of a new guideline (the Q&A Procedure), the revision or modification of existing guidelines (the Revision Procedure), and the addition of standards to existing guidelines and recommendations (the Maintenance Procedure).³⁵⁷

In developing harmonised guidelines (the Formal ICH Procedure), the ICH follows a five-step consultative mechanism.³⁵⁸ The process is triggered by one of the members or non-voting observers, which presents a ‘Concept Paper’ on the issue at stake to the SC.³⁵⁹ Once the SC has endorsed the Concept Paper, an Expert Working Group (EWG) drafts a preliminary guideline based on the Concept Paper’s desired goals. After the preliminary guideline has been approved by the SC, it undergoes regulatory consultation processes in the three regions (US, EU, Japan). The key actors at this stage become the regional agencies responsible for the consultation process. In particular, the FDA carries out the notice and comment procedure set out in the FDA’s Good Guidance Practice.³⁶⁰ The EMA follows its Procedure for Guidelines and provides for a public

³⁵⁵ Follow the ‘Organisation of ICH’ and then the ‘Steering Committee’ hyperlink from the ‘About ICH’ section on the ICH website.

³⁵⁶ Follow the ‘Organisation of ICH’ hyperlink from the ‘About ICH’ section on the ICH website.

³⁵⁷ For a full description follow the ‘Process for Harmonisation’ hyperlink from the ‘About ICH’ section on the ICH website.

³⁵⁸ All decisions, both in the Steering Committee and in the subordinate working groups, are taken by way of consensus.

³⁵⁹ See the full description of the process by following the ‘Process of Harmonisation’ and then the ‘Formal Procedure’ hyperlinks from the ‘About ICH’ section on the ICH website.

³⁶⁰ 21 CFR 10.115: a detailed overview of the domestic consultation procedure in the US is available in Berman A., “The Role of Domestic Administrative Law in the Accountability of IN-LAW: The Case of ICH”, in Pauwelyn J., Wessel R.A., Wouters J. (eds.), *Informal International Lawmaking*, Oxford University Press, 2012, pp. 468-499.

consultation mechanism.³⁶¹ Comments can however also be submitted directly to the ICH, and the WHO circulates the draft guidelines among its members for comments and observations. Commenting is therefore open to anyone from any country interested in taking part in the discussion. The results of the consultations are sent back to the ICH EWG, which elaborates, on the basis of the received comments and observations, an amended draft guideline to be adopted by the SC as a harmonised ICH Guideline. The Guideline is subsequently adopted domestically by each member.

While the commenting procedure is conceived as open and inclusive, the deliberative mechanisms are exclusive and scarcely transparent, as the proceedings of the SC and the negotiation processes are not published. While there is some access to the preliminary stages of consensus-building, actual decision-making is left to the internal mechanisms, and the lack of access to the SC's internal proceedings does not allow for a full appreciation or evaluation of the fate of regional consulting results.

The final stage of the five-step Formal ICH Procedure, implementation, is in the hands of the regional agencies, which adopt the ICH Guidelines for the conduct of internal marketing approval procedures (*within* the legal framework governing the margins of autonomy of agencies for their rule-making activity, but *outside* the rule-making mechanisms domestically in place).³⁶² While ICH Guidelines are accepted as generally legally non-binding, it is arguable that they can be considered *de facto* binding³⁶³ – despite their origin in open negotiations with industry – due to the nature and extent of their use at a domestic level.³⁶⁴ The *de facto* binding role of ICH Guidelines is strikingly suggested by the heavy reliance on these Guidelines by national lawmakers designing domestic and regional legislation. The ICH E6 Guideline on GCP, discussed above, has been essentially

³⁶¹ EMA, “Procedure for European Union Guidelines and Related Documents within the Pharmaceutical Legislative Framework”, 2009, Doc. Ref. EMEA/P/24143/2004 Rev. 1, available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004011.pdf.

³⁶² In the example of GCP, the Guideline was adopted by the FDA and published in the Federal Register, 9 May 1997, Vol. 62, No. 90, p. 25691-25709; and by the EMA in July 1996, issued as CPMP/ICH/135/95/Step 5, and subsequently translated into Directive 2005/28/EC as a consolidated administrative practice. Whereas in both cases the preliminary guideline underwent the comment consultation procedures, the final outcome is the result of a further negotiation which is not accounted for as the proceedings are exclusive and not accessible.

³⁶³ See Purnhagen K., “Competition of Agencies in European Pharmaceutical Law – Does It Exist, Is It Desirable and How to Handle It?”, *European Journal of Risk Regulation*, 1, 2010, pp. 227-238

³⁶⁴ See Purnhagen K., “The Challenge of Globalization in Pharmaceutical Law”, and Krapohl S., *Risk Regulation in the Single Market*, Palgrave Macmillan, 2008, p. 86 ff.

fully adopted in both the European Directive 2001/20/EC on Good Clinical Practice and the amended US 21 CFR 312. As described in section 1, that Guideline now constitutes the legal basis for acceptance of foreign data in the major pharmaceutical markets. The majority of ICH Guidelines do not end up being adopted as formal acts of law: they instead remain in the domestic legal framework as policy documents (for example, administrative updates of the existing regulatory system) or instruments of ‘governance’ (which are not strictly speaking legal).³⁶⁵ But when agencies, for example, interpret national pharmaceutical law, they consult ICH Guidelines and interpret the respective national rules and procedures in their light. The domestic impact of such guidelines, in light of the analysis proposed in chapter III, can therefore be dramatic.

ICH is therefore, in summary, a trilateral technical forum between the regulatory authorities and pharmaceutical companies of the EU, US, and Japan. The industry and regulators have found their interests converging over the last two decades, with a mutual desire to reduce the use of “human, animal and material resources” as they work to “eliminate unnecessary delay in the global development and registration of new drugs”.³⁶⁶ The opportunity to cut costs and draw from large pools of potential patients is a potent driver for globalising pre-marketing procedures, as previously discussed. Criticisms have long been levied against the FDA for taking too long to review and approve drugs, and despite its shorter period of activity, similar complaints have been raised regarding the EMA.³⁶⁷ The opportunity to concretise market pressures into a set of regulatory guidelines represents the way for Western agencies to lessen their burden, and for the industry to substantially cut costs and delays in new products approvals.³⁶⁸ The answer to the question

³⁶⁵ We will discuss this phenomenon *infra* but for a general discussion see Berman A., “Informal International Law Making in Medical Products Regulation”; and on the questionable legitimacy of these practices Ehnert T., “The Legitimacy of New Risk Governance – A Critical View in Light of the EU’s Approach to Nanotechnologies in Food”, *European Law Journal*, doi: 10.1111/eulj.12082 (April 16, 2014). The author relies on traditional concepts of legitimacy as elaborated by Habermas and Scharpf to demonstrate the lack thereof in European risk governance.

³⁶⁶ Purnhagen K., “The Challenge of Globalization in Pharmaceutical Law”, quoting Hoff S., “The Regulatory Environment for the New Millennium”, *Drug Information Journal*, 34, 2000, pp. 659-72.

³⁶⁷ Andersson F., “The Drug Lag Issue: The Debate Seen from an International Perspective”, *International Journal of Health Services*, 22, 1998, pp. 53-72.

³⁶⁸ A goal clearly stated by the ICH itself: “Regulatory harmonisation offers many direct benefits to both regulatory authorities and the pharmaceutical industry with beneficial impact for the protection of public health. Key benefits include: preventing duplication of clinical trials in humans and minimising the use of animal testing without compromising safety and effectiveness; streamlining the regulatory assessment process for new drug applications; and reducing the development times and resources for drug development”: follow the ‘Vision’ hyperlink from the ‘About ICH’ section on the ICH website.

on who makes the fundamental choices finds its answer in the hardly measurable negotiation process within the ICH Steering Committee, whose members act within broad legislative frameworks leaving them ample margins of manoeuvre – originally conceived for domestic mechanisms and therefore scarcely equipped for transnational permeations.

3. An experimentalist new mode of governance domestically, a non-inclusive model transnationally

Describing which type of governance model (among those suggested and analysed in a quite florid literature³⁶⁹) is in place in the pharmaceutical system is a rather difficult endeavour. This section proposes an interpretation that expands on a claim raised at the beginning of this study and restated in the previous chapter: that pharmaceutical regulation is mostly understood as a domestic phenomenon, to the extent that it is also generally studied as such. The international dimension somehow escapes the legal scholarship debate and yet undermines, at least partially, the conclusions reached in the analysis of domestic governance. When pharmaceutical regulation *is* studied as an international phenomenon, the analysis often limits itself to the observation of international soft law-making mechanisms without clearly linking those mechanisms to their domestic impacts.³⁷⁰ What is missing, then, is a study of the implications of transnational regulation for domestic systems of governance.

Chapter II described how advisory committees have over time gained power, going far beyond consultancy and becoming real policy-makers. We have referred to this phenomenon as a ‘capture’ of regulatory power. This process has been described in many and different ways. One of the most comprehensive accounts of the evolution of administrative law has been provided by Karl-Heinz Ladeur, who depicts thoroughly how

³⁶⁹ A complete account of the debate over transnational models of governance goes far beyond the scope of this work. For an overview see Maduro M., Tuori K., Sankari S., *Transnational Law – Rethinking European Law and Legal Thinking*, Cambridge University Press, 2014; Kingsbury B., Krisch N., Stewart R. (special eds.), “The Emergence of Global Administrative Law”, *Law and Contemporary Problems*, Vol. 68 n° 3 & 4, 2005; Sabel C.F., Zeitlin J., “Learning from Difference: The New Architecture of Experimentalist Governance in the EU”, 14 *European Law Journal* 3, 2008; Joerges C., Dehousse R. (eds.), *Good Governance in an Integrated Market*, Oxford University Press, 2002; Scott J., Trubek D.M., “Mind the Gap: Law and New Approaches to Governance in the European Union”, 8 *European Law Journal* 1, 2002; Walker N., de Burca G., “Reconceiving Law and New Governance”, 13 *Columbia Journal of European Law* 519, 2007.

³⁷⁰ See for example for the international level the literature cited in this chapter by Purnhagen and Berman, and for the domestic level see in Europe Feldschreiber and Howells.

this process of power attraction by administrators is an inherent trait of administrative law since its very origins. In this interpretation, such a process (which leads to the phenomenon of *autopoiesis* of norms by administrative authorities)³⁷¹ is natural and may find its balance in terms of legitimacy through experience, insofar as administrative law is much more the result of administrative experimentation (and subsequent judicialisation) than the output of a legislative mechanism. To consider administrative law as a self-generating endeavour, only at a subsequent stage stabilised by courts or the legislators, allows for an interpretation that focuses on the societal dynamics that lead the evolutionary process of norm self-generation.³⁷² In this regard, societal dynamics are described as moving from the ‘society of individuals’ intimately linked with a form of administrative law based upon individual decisions, a stage that coincides in the language of statecraft with the age of the ‘state-nation’.³⁷³ The following stage runs in parallel with the move to the ‘nation state’, and as such is defined as the ‘society of organisations’, where individual decisions give way to more collective concerns such as planning laws and forms of welfare state. Subsequently, as the state has moved to its most recent evolution, referred to as the ‘market state’, societal dynamics have evolved to the current ‘network society’, which requires new administrative forms and procedures for decision-making.³⁷⁴ The core idea of Ladeur’s theory is that:³⁷⁵

the globalization process does not invade a stable domestic administrative [...] legal system from outside, but that it is also a consequence of an evolutionary process that disrupts the legal system from within.

According to this idea, the move from domestic to transnational is a natural process which is consistent with national experiences, as it is considered to be a consequence of the societal dynamics that led to the kind of global networking of which the ICH is a perfect example. To an extent, the evolution in three phases of pharmaceutical regulation which we are describing in these chapters is compatible with this evolutionary theory of administrative law. However, we contend that a general objection

³⁷¹ See Ladeur K.-H, “The Emergence of Global Administrative Law and the Evolution of General Administrative Law”, *Comparative Research in Law & Political Economy*, Osgoode Hall Law School, Research Paper n°16/2011.

³⁷² *Ibidem*, p. 5 ff.

³⁷³ We use here the evolution of statecraft as described extensively by Bobbitt: see Bobbitt P., *The Shield of Achilles*, Anchor Books, 2003, Book I Parts II & III; see reference made in the Introduction.

³⁷⁴ Ladeur K.-H, “The Emergence of Global Administrative Law and the Evolution of General Administrative Law”, p. 24 ff.

³⁷⁵ *Ibidem*, p. 6.

can be raised to this idea of the evolution of administrative law, specifically focusing on our field of interest. If it is true that regulators and regulated have always discussed the terms of the rules (and they have, within a given legislative framework, as described in chapter II), the international dimension here introduces a rather new and different phenomenon. The regulators and the industry are participating *as peers* in the elaboration of ICH Guidelines – guidelines that contribute themselves to the shaping and implementation of national or regional norms (for instance in the case of GCP). Such a situation is hardly comparable to general administrative law as traditionally conceived in Western democratic nation states.³⁷⁶ To exclusively describe the contemporary state of administrative law as reflecting the natural course of societal dynamics runs the risk, from a legal standpoint, of underestimating the profoundly different context in which the ‘networks’ are operating (uncharted transnational territories)³⁷⁷ as opposed to the ‘organisations’ (previously operating in national or regional constitutionally and legally defined domains).

A different line of thinking, in the attempt to create a theoretical justification for the escape of regulatory mechanisms from traditional modes of democratic legitimation, has elaborated the idea of “experimentalist new governance”.³⁷⁸ The basic premise of this theory grounds the legitimacy of regulatory models in an alternative way to traditional representative democratic circuits, through the concept of ‘deliberation’. A deliberative process is a ‘soft process’, including all the major stakeholders of a given field, in which governance is achieved in *functional* rather than traditional *structural* or *institutional* terms.³⁷⁹ Charles Sabel and Jonathan Zeitlin observe that such a soft consultative process can only

³⁷⁶ For a complete account of traditional Western concepts of administrative regulation see above all Ogas A., *Regulation: Legal Form and Economic Theory*, Hart Publishing, 2004; and in comparative perspective see Rose-Ackerman S., Lindseth P.L. (eds), *Comparative Administrative Law*, Edward Elgar, 2011.

³⁷⁷ Consider the example of the ICH: no administrative agency in the US, nor in the EU, would ever be constructed in a way that a) involves only one-sided stakeholders together with the regulators; and b) lacks clear procedural rules on transparency, participation and access to documents. But its informal nature, and the context in which it operates (the uncharted transnational territories), allow for greater flexibility. Arguably, the ICH exists *because* at a transnational level negotiations can happen in a much less scrutinised fashion.

³⁷⁸ See the essential contribution of Sabel C.F., Zeitlin J., “Learning from Difference: The New Architecture of Experimentalist Governance in the EU”, 14 *European Law Journal* 3, 2008, pp. 271-327; see also the recent interesting contribution by De Burca G., Keohane R.O., Sabel C., “Global Experimentalist Governance”, *British Journal of Political Science* 44, 2014, pp. 477-486.

³⁷⁹ *Ibidem*, p. 274.

legitimise itself by adherence to “standards of some alternative deliberative democracy”.³⁸⁰ Typically, the deliberative democratic process is described as informal, as the socialisation of stakeholders involved in the decision process (something referred to as “epistemic communities” – for instance the comitology mechanisms of the EU) does not necessarily descend directly from legislative acts.³⁸¹ It is also considered (in its European variety) to be ‘multi-level’, as it involves actors ranging from national administrations to supra-national bodies without establishing a hierarchy between them, blurring the distinction between centralised and decentralised decision-making and instead favouring networks of diverse decision-makers.³⁸² Moreover, to overcome the most immediate criticism identifiable in the departure from representative democracy’s classic forms of accountability and legitimacy, the deliberative process is essentially inspired by principles of transparency, access, and participation.³⁸³

It has been argued that pharmaceutical regulation falls within the scope of ‘experimentalist new governance’ because the agencies involved (we consider here the FDA and the EMA) are built in a way that includes all stakeholders involved in the pharmaceutical market. Both agencies recognise a central role for scientific committees, and these committees are assisted by various actors, such as representatives of patients, physicians, and the government.³⁸⁴ Decisions within the agency bodies are taken by way of consensus through deliberation as much as possible, with voting being the last resort option.

As intriguing as this suggestion may be, we posit that it falls short of addressing properly the issue of transparency, which *per se* undermines the conclusion. We have

³⁸⁰ *Ibidem*, p. 273 – recognising that even strong advocates of the model struggle to reach a positive conclusion.

³⁸¹ As observed among others by Neyer J., “Explaining the Unexpected: Efficiency and Effectiveness in European Decision-Making”, 11 *Journal of European Public Policy* 19, 2011.

³⁸² See Sabel C.F., Zeitlin J., “Learning from Difference”, p. 273; and the essential contributions cited in the piece by Egeberg M. (ed.), *Multilevel Union Administration: The Transformation of Executive Politics in Europe*, Palgrave Macmillan, 2006, and Hofmann H.C.H., Türk A.H. (eds.), *EU Administrative Governance*, Edward Elgar, 2006.

³⁸³ A recent, interesting, and comprehensive discussion can be found in Ehnert T., “The Legitimacy of New Risk Governance”.

³⁸⁴ We refer by way of example to the Management Board of the EMA, which originally comprised two representatives of the Commission, two members of the European Parliament, and one representative per MS. With the essential reforms brought by Directive 2001/83 and Regulation 726/04 the Board was extended to comprise members from interest groups including patients and physicians. In the US, the Advisory Committees of the FDA similarly include physicians, consumers, and insurance companies.

discussed the issue of access to clinical trials data. If it is true that *ex ante* rule-making transparency mechanisms, on the one hand, and on the other hand *ex post* access to processed data are very different things, nonetheless it seems hardly conceivable that an ‘alternative deliberative democracy’ can be founded on restricted access to essential information, protected under trade considerations. The reason for this claim is that the *functional* legitimacy of deliberative democracy mechanisms is grounded on fundamental principles of transparency, participation, and access. If the final output of the process, that is the regulated product, cannot be evaluated in full (as is the case when the clinical trial history of a medicine cannot be traced by reason of non-accessibility of data), the transparent mechanism of rule-adoption is rendered void by the impossibility of evaluating its effectiveness in achieving the purported goals.³⁸⁵

If the potential for domestic regulatory mechanisms to fall within the scope of an experimentalist mode of governance can in theory be argued, such hypothesis does not fully confront the transnational dimension and its implications. The descriptions of the ICH mechanisms, and of the substantial impact of its guidelines, strongly point to the necessity of moving the reflection to a transnational level. At that transnational level, the rule-making mechanism is structurally non-inclusive, and modelled around goals set by a restricted number of stakeholders. We have argued that the basic value-choice is trade-oriented, and that no real counterpart is involved in the negotiation process. The fundamental Guidelines on GCP are a good example of a procedural regulation, leaving a wide margin of appreciation in the substance of the standards, which has been adopted ‘blindly’ by agencies supposed to ensure deliberative processes.³⁸⁶ The mechanisms of production and adoption of ICH Guidelines do not appear to be conceived to balance the disproportionate margin of discretion the new-governance agents benefit from *vis à vis* traditional rule-makers in representative democratic circuits. The scenario as described throughout this chapter suggests rather that there is (in the field of pharmaceutical regulation) a tendency to ‘hollow out’ procedural standards when the scene is set at the transnational ICH level.³⁸⁷ Strong domestic procedural mechanisms, accepted as legitimate

³⁸⁵ See the discussion of the idea of credible commitment in section 4 of this chapter.

³⁸⁶ There is no real access to information about what participation has been guaranteed in the adoption process of the GCP Guidelines, either by the FDA or the EMA – the internal ICH documents are not accessible, only the final Guidelines are. What is striking, on the other hand, is the ultimate literal transplant of said Guidelines into legislation.

³⁸⁷ The issue is well raised in Mendes J., “EU Law and Global Regulatory Regimes: Hollowing Out

and effective in principle, may appear thus to be circumvented.

The above discussion on the model of governance in place for the regulation of pharmaceutical products suggests uneasy answers. While designed and described as an example of ‘new governance’ domestically, as a transnational phenomenon it appears to resemble more a reversed version of the transnational private law (TPR) theory elaborated by Gralf-Peter Calliess and Peer Zumbansen in “Rough Consensus and Running Code”.³⁸⁸ While the theory proposes an understanding of bottom-up societal regulation of TPR, the pharmaceutical system seems to be organised in a top-down fashion, whereby the consensus and the running code are reached and infused in the regulatory mechanisms by selected stakeholders and interests, with what we have referred to in the opening chapter of the thesis as the idea of a *closed and self-perpetuating system*. This re-opens the question of the source of legitimacy for the pharmaceutical regulatory system, and presents a rather difficult case for any attempt to ground such legitimacy at the *ex ante* rule-making stage.

4. The source of legitimacy – a credible commitment in the absence of participatory mechanisms?

If legitimacy is hard, if not impossible altogether, to achieve at the rule-making stage, different mechanisms must be conceived. The attempt is to legitimise *ex post* the regulatory framework by evaluating its success in achieving its goals: a form of output-based legitimacy used to circumvent and overcome the absence of the more traditional input-based one.³⁸⁹ Chapter III raised several issues in terms of transparency and access to clinical trials data. We have already argued that if essential data are non-accessible, the evaluation of output is a complex (if not forlorn) task. The new EU

Procedural Standards?”, 10 *International Journal of Constitutional Law* 4, 2012, pp. 988-1022; see the more recent discussion on internationalised rule-making mechanisms Mendes J., “Rule of law and participation: a normative analysis of internationalised rulemaking as composite procedures?”, *International Journal of Constitutional Law* 12, 2014, pp. 370-401.

³⁸⁸ Calliess G.-P., Zumbansen P., *Rough Consensus and Running Code – A Theory of Transnational Private Law*, Hart Publishing, 2010. The theory is based on the idea that a *Rough Consensus* among stakeholders in a given field becomes a *Running Code* through a *pilot phase* in which the content of the consensus acts as a proposed standard, followed by a *recognition phase* in which the standard becomes recommended, and eventually a *binding phase* where the standard is adopted. The process, being inclusive and non-hierarchical, is eminently bottom-up.

³⁸⁹ See again the discussion in Ehnert T., “The Legitimacy of New Risk Governance”; the classic arguments in Scharpf F. W., *Governing in Europe: Effective and Democratic?*, Oxford University Press, 1999; see also the interesting Bartl M., *Legitimacy and European Private Law*, EUI Thesis, 2012.

Clinical Trials Regulation referred to in the previous chapter might make a difference in the future (for new MAAs),³⁹⁰ but for the time being, access to data for currently marketed medicines remains largely restricted.

It is possible however to look at the final safety outcome (that is, the safety or actual harms attributed to products marketed under a certain regulatory framework). It is then possible to a certain extent to evaluate and legitimise a certain regulatory framework by reference to that outcome. An essential contribution to this line of thinking comes from the theory of “credible commitment” as elaborated by Giandomenico Majone and developed by Sebastian Krapohl.³⁹¹ The idea is that either through delegation or through legislation, regulators gain substantial policy-making power, which they exercise independently, within a general legal framework setting the goals of the regulatory system to which they commit themselves.³⁹² Because the decision-making of such regulatory regimes cannot be legitimised by input from democratically elected bodies, it must legitimise itself through the efficiency and efficacy of its policy outputs.³⁹³ A common culture and a common interest arise among regulators to efficiently pursue the scope of their activity, thus triggering a positive effect on the quality of the output. However, such a theory is again designed for domestic and/or regional scenarios, and pharmaceutical regulation is instead a transnational one.

To the extent that the effectiveness of outputs necessitates a common interest and culture, the description of the ICH previously suggested raises some concerns. It must be recalled that the ICH is, partially, a transnational regulatory network (TRN),³⁹⁴ and partially a hybrid body involving regulators and industry as peers. Participation is restricted to national regulators appointed by their respective authority of origin, coupled with representatives of the pharmaceutical industry. As regards the national regulators it has been argued that “[f]ar from being removed from domestic politics, regulators are tied to them by multiple channels [linked to domestic interests] that generally outweigh their

³⁹⁰ See the discussion of the adoption of Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.05.2014, pp. 1–76.

³⁹¹ Krapohl S., *Risk Regulation in the Single Market*; Majone G., *Regulating Europe*, Routledge, 1996.

³⁹² Krapohl S., *Risk Regulation in the Single Market*, pp. 43-50.

³⁹³ Majone G., *Regulating Europe*, pp. 284-301.

³⁹⁴ A critical analysis of transnational regulatory networks can be found in Verdier P.H., “Transnational Regulatory Networks and their Limits”, 34 *Yale Journal of International Law* 113, 2009.

loyalty to global interests”.³⁹⁵ Such ties create a series of conflicts of interest between constituents, and thus an obstacle to the creation of a common interest, which undermines the quality of the result. Issued harmonising guidelines may accordingly pose risks of a race-to-the-bottom in standards adoption, or simply avoid critical topics. The specificity and complexity of this field is also fostered by the presence of divergent ‘therapeutic cultures’. These create a series of frictions based on different understandings of key notions that lie at the very basis of safety regulation (such as, again, the notion of risk, aversion to or embracing of it).³⁹⁶ Not only conflicts among different national interests and divergent therapeutic cultures have to be considered. The ICH scheme includes (together with the regulators, in equal numbers and with equal powers) the strong presence of the industry, which brings a clear-cut trade drive into the equation that can hardly be accounted for. Under the given circumstances, it appears difficult to apply the criterion of ‘credible commitment’, which could operate as a substitute for democratic and deliberative legitimacy, to the ICH. Nor does it appear reasonable to expect the creation of a “transnational legal culture”³⁹⁷ in the field, as fundamental divergences over the substance of the issues to be regulated persist.³⁹⁸

When it comes to pharmaceutical regulation, the generally accepted policy objectives are twofold: access to medicines and protection of health and safety.³⁹⁹ Evaluating the output of the regulatory system as legitimate entails an analysis of both elements. While elements of the first aspect have been discussed in both chapter III and in the previous sections of this chapter (to the extent that the transnationalisation of procedures and rule-making mechanisms facilitates its achievement), the analysis of health and safety outcomes will be the object of the following chapter V.

³⁹⁵ Verdier P.H., “Transnational Regulatory Networks and their Limits”, p.162; *contra* see Slaughter A.M., *A New World Order*, Princeton University Press, 2004, pp. 131-162; see also the recent Fenwick M., Van Uytel S., Wrba S. (eds), *Networked Governance, Transnational Business and the Law*, Springer, 2014.

³⁹⁶ See section 3 of chapter III.

³⁹⁷ The idea is suggested by Tuori K., “Towards a Theory of Transnational Law” (unpublished paper, 26 August 2010); see also the discussions in Maduro M., Tuori K., Shankari S., *Transnational Law – Rethinking European Law and Legal Thinking*, Cambridge University Press, 2014.

³⁹⁸ We refer again to the analysis proposed in chapter III, and to sections 1 and 2 of this chapter.

³⁹⁹ The objectives are stated as for the EU in Directive 2001/83/EC, and as for the US in 21 CFR 312 ff.

CHAPTER V

QUESTIONING THE INSTITUTIONAL DESIGN 3

EVALUATING THE SAFETY OUTCOME

The conclusions of chapters III and IV call for an evaluation of the safety outcomes provided by the pharmaceutical regulatory system as currently designed. What follows is a selection of case studies aimed at determining whether there are deficiencies in pre-marketing regulation hindering the goal of product safety, and whether the post-marketing management and surveillance systems as provided by the current regulatory framework are sufficient to overcome the issues of substantive uncertainty and procedural ‘democratic deficit’. Developing the issues discussed in chapters III and IV, the analysis of the safety outcome attempts an evaluation of the efficacy of the system and, therefore, of its output-based legitimacy.

1. Vioxx and Celebrex - Randomised risk discovery

The first element to consider is the effectiveness of the pre- and post-marketing regulatory schemes in identifying risks related to medicinal products. To what extent are regulatory schemes effective in capturing risks to consumer health? To fully understand the centrality of the issue this section will analyse a well-known case of regulatory failure: *Rofecoxib*, commercially distributed by its manufacturer Merck as Vioxx.⁴⁰⁰ This case is of marked interest as it reveals in a relatively straightforward way a series of weak spots in the regulatory mechanisms leading to marketing approval and providing for post-marketing surveillance. It is worth noting that as a result of the Vioxx crisis, both the US (in 2007

⁴⁰⁰ A very detailed historical account is provided by FDA, “Sequence of Events with Vioxx Since Opening of IND”, available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_04_E-FDA-TAB-C.htm; the account has been further developed by Gilhooley M., “Vioxx’s History and the Need for Better Procedures and Better Testing”, *Seton Hall Law Review* 37, 2007, pp. 945-954.

and 2012)⁴⁰¹ and shortly thereafter the EU (in 2010 and 2012)⁴⁰² have reacted with the adoption of revised procedural requirements both pre- and post-marketing. It has been argued (and the final section of this chapter will expand on this claim) that the new provisions, while correctly identifying the issues to redress, fall short of effectively addressing the structural causes of the crisis.⁴⁰³ Other subsequent cases such as *Rosiglitazone* (commercial name Avandia, analysed in section II of this chapter) or *Benfluorex* (commercialised under various denominations, the most controversial one being Mediator in France),⁴⁰⁴ support the concern that regulatory mechanisms are, on their own, insufficient to optimally⁴⁰⁵ confront the emergence of risks to consumer health.

The history of Vioxx can be recounted as of its first marketing approval in the US, on the 20th of May 1999⁴⁰⁶ (approval in the EU followed shortly through a mutual recognition procedure, the UK being the Reference Member State).⁴⁰⁷ Vioxx was approved by the FDA to treat severe and chronic pain in patients suffering arthritis. The key feature offered by Vioxx and other drugs of the same category, known as COX-2 inhibitors (such as *Celecoxib* marketed as Celebrex by Merck's competitor Pfizer), was a significant gastrointestinal advantage as compared to other arthritis pain relievers already in the market.⁴⁰⁸ A first element to note (one which is of relevance to the development of this historical reconstruction) is that despite its clear intent to provide a comparative advantage, Vioxx was never tested against its pre-existing competitors for marketing approval, but

⁴⁰¹ The Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 110 Stat. 823.

⁴⁰² Regulation (EU) 1235/2010 of the European Parliament and of the Council amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) 726/2004, and Directive 2012/26/EU of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance (text with EEA relevance), OJ 2012 L 299/1.

⁴⁰³ The principal reason being a significant lack of funding which makes comprehensive post-marketing surveillance no more feasible than before, see *infra* section 3.

⁴⁰⁴ Mediator, commercialised by Servier, was prescribed to patients with type-2 diabetes to reduce insulin resistance (a so called 'adjuvant antidiabetic'). It is an old medicine first marketed in 1976 that remained on the market until the EMA in 2009 recommended its withdrawal due to related risks of cardiovascular events – see EMA, Benfluorex art. 107 referral, Annex II, available at http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Benfluorex_107/WC500109589.pdf.

⁴⁰⁵ See chapter I on the idea of the 'optimal' enforcement of the law in the field.

⁴⁰⁶ FDA letter of approval NDA 21-042 of May 20th 1999, retrievable from the Vioxx 'Drug Approval Package', at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-042s007_Vioxx.cfm.

⁴⁰⁷ Vioxx was approved in the UK in June 1999, as confirmed in private correspondence with the Medical Writer of the FOI team, Licensing Division of the MHRA.

⁴⁰⁸ Although such significant advantage was only proved later on by the VIGOR study as discussed *infra*, and therefore the comparative advantage was initially only theoretical – which questions the appropriateness of the marketing authorisation, see Gilhooley M., "Vioxx's History", pp. 945-947.

only against placebo.⁴⁰⁹ While cardiovascular risks were considered “theoretically” possible,⁴¹⁰ this possibility was not reflected in the data submitted to the agency for approval, as the evidentiary basis was not considered sufficient.⁴¹¹ The FDA (and subsequently the UK MHRA) was satisfied with the safety database for Vioxx, which was considered robust and as fulfilling regulatory requirements for approval.⁴¹² The absence (real or purported – the impossibility of fully accessing the clinical trial history of the drug makes it difficult to say with certainty) of “evidentiary concerns” about cardiovascular ADRs prompted an approval without any reference to such potential risks in the labelling.⁴¹³

Interestingly, the existence of severe cardiovascular risks, which triggered the subsequent unfolding of events (worldwide withdrawal of the drug and widespread law suits resulting in multi-billion dollar settlements),⁴¹⁴ was discovered thanks to a voluntary initiative of Merck itself. As recalled, the major advantage COX-2 inhibitors were supposed to offer compared to pre-existing competitors was reduced gastrointestinal risk, or more accurately, a reduced risk of stomach bleeding.⁴¹⁵ After approval had been granted, Merck undertook a post-marketing study (referred to as a ‘clinical study outcome’,

⁴⁰⁹ As prescribed by standard procedure in NDAs: see again the information available in the Vioxx ‘Drug Approval Package’, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-042s007_Vioxx.cfm.

⁴¹⁰ The concern is raised by the NDA Reviewer whose assessment is contained in the Excerpts from Primary Review of NDA 21-042 Osteoarthritis 9 (1999), available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_05_F-FDA-Tab-D-1.pdf, suggesting the need for a larger database to clarify whether cardiovascular and thromboembolic events increased in patients due to *Rofecoxib* – the datapool available for drug approval was statistically insufficient on the matter.

⁴¹¹ *Ibidem*.

⁴¹² FDA letter of approval NDA 21-042 of May 20th 1999, retrievable from the Vioxx ‘Drug Approval Package’, at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-042s007_Vioxx.cfm; see also Jümi P. et al., “Risk of Cardiovascular Events and Rofecoxib: Cumulative Meta-Analysis”, *The Lancet* 364, 2004, pp. 2021-2029.

⁴¹³ See the original Vioxx label of 1999, retrievable from the Vioxx ‘Drug Approval Package’, at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-042s007_Vioxx.cfm. The label did contain a warning against potential stomach bleeding as the evidence emerging from pivotal pre-marketing trials were insufficient to prove a statistically comparative progress from available therapies such as *Naproxen*. The VIGOR study discussed *infra* was designed precisely to consolidate the claim to gastrointestinal comparative safety.

⁴¹⁴ The legal repercussions of the Vioxx case are analysed in greater detail *infra* in the final section.

⁴¹⁵ Following the Vioxx unfolding of events, a series of hearings were held before the Senate to assess the responsibility of the manufacturer and of the agency. The expectations of gastrointestinal safety were reported in the hearing: *The FDA, Merck and Vioxx: Putting Patient Safety First: Hearing Before the Senate Finance Committee*, 108th Cong., 2004. This was only a prospect at the approval stage; confirmation only arrived with the results of the VIGOR study, see *infra*. As previously noted, the absence of relevant data on either cardiovascular safety or gastrointestinal advantages raises questions over the approval of Vioxx for marketing in the first place.

as opposed to ‘pivotal studies’ which form the basis for approvals) to evaluate its benefits and reduced risk of bleeding in comparison to the previously successful anti-arthritis drug *Naproxen* (commercialised by Roche Pharmaceuticals as Naprosyn). The study, known as the VIGOR study,⁴¹⁶ confirmed the comparative benefits of Vioxx as regards gastrointestinal complications but also showed an increase in risk of cardiovascular events ranging from heart attacks to strokes.⁴¹⁷ The results showed an increased risk for a dosage of 50mg which had only been approved to treat severe pain, the regular dosage being 25mg.⁴¹⁸ VIGOR’s results induced the FDA to solicit Merck to undertake a specific clinical study purposely directed at evaluating cardiovascular ADRs.⁴¹⁹ Merck refused on “ethical and logistical” grounds⁴²⁰ and suggested that an evaluation of cardiovascular ADRs to Vioxx would emerge from the separate clinical study APPROVe, launched in 2000 by Merck to investigate the potential of Vioxx as an alternative treatment for colon cancer.⁴²¹ While the results of the VIGOR study were presented to the FDA in March 2000, it was only in 2002 that a revised label was approved to warn consumers of the potential cardiovascular risks that had emerged in the study.⁴²² Controversy ensued, with the adoption of the labelling agreed upon after prolonged negotiations between Merck and the FDA containing wording that arguably understated the real extent of the potential harm.⁴²³

⁴¹⁶ Acronym for Vioxx Gastrointestinal Outcomes Research Trial.

⁴¹⁷ See Bombardier C. et al., “Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis”, 343 *New England Journal of Medicine*, 2000, pp. 1520-1528.

⁴¹⁸ As per the original Vioxx label of 1999, retrievable from the Vioxx ‘Drug Approval Package’, at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-042s007_Vioxx.cfm.

⁴¹⁹ For a critical account of how the FDA initially required specific trials to measure cardiovascular risk but subsequently backed off, see Topol E.J., “Failing the Public Health—Rofecoxib, Merck, and the FDA”, 351 *New England Journal of Medicine*, 2004, pp. 1707-1708.

⁴²⁰ Gilhooley M., “Vioxx’s History”, p. 947, referring to the testimony of Dr. Sandra Kweder of the FDA in the recalled *Hearing Before the Senate Finance Committee*.

⁴²¹ Acronym for Adenomatous Polyp Prevention on Vioxx Trial.

⁴²² The modifications can be appreciated in the 2002 amended version of the label, retrievable from the Vioxx ‘Drug Approval Package’, at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-042s007_Vioxx.cfm.

⁴²³ The new labelling introduced in a specific section, ‘Precautions’, a warning that “caution should be exercised when Vioxx is used in patients with a medical history of ischemic disease”, see 2002 label *ibidem*. The wording is arguably vague and insufficient to adequately warn consumers. In negotiating the wording, Merck relied on the argument that since no specific studies on cardiovascular ADRs had been carried out, the real incidence of Vioxx in cardiovascular ADRs was effectively unknown. See Gilhooley M., “Vioxx’s History”, p. 948; Topol E.J., “Failing the Public Health”, p. 1707; *Hearing Before the Senate Finance Committee*.

Two years later, in 2004, while investigating Vioxx's potential to prevent colon cancer, the APPROVe study began to show a statistically significant increase in the risk of cardiovascular ADRs, this time linked to the 'regular' 25mg dosage (which was prescribed not for severe, but chronic pain).⁴²⁴ It is at this stage that, on the 30th of September 2004, Merck decided to voluntarily withdraw the product worldwide,⁴²⁵ as APPROVe constituted for Merck the first solid database of actual cardiovascular risk linked to Vioxx consumption.⁴²⁶

For the purposes of our chapter, that is analysing the safety output of regulatory mechanisms (specifically in this section the structural fitness of pre-market rules to allow the emergence of assessment-relevant knowledge, and conversely the ability of post-marketing surveillance duties to facilitate and react to supervening risk discoveries), this brief historical account uncovers at least three critical elements.

First, the initial emergence of a potential cardiovascular risk for high doses of 50mg was completely casual. What enabled it was Merck undertaking a study aimed at proving a comparative advantage over a pre-existing treatment as regards gastrointestinal complications (the very reason why COX-2 inhibitors had been successfully marketed in the first place). The definitive proof of increased danger extending to the lower dose of 25mg came from another study evaluating potential alternative therapeutic benefits of the drug. In other words, it took independent research conducted by Merck itself for purposes that had nothing to do with safety evaluation to make the risk emerge. While it is common for new risks to emerge in the course of unrelated studies,⁴²⁷ it is the ability of the pharmacovigilance system to facilitate new risk discoveries independently from data voluntarily gathered by the manufacturer that is in question here. Pre-marketing approval testing was only able to identify the potential harm at a theoretical level, as suggested

⁴²⁴ The full study appeared in early 2005 by Bresalier R.S. et al., "Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial", 352 *New England Journal of Medicine*, 2005, pp. 1092-1102.

⁴²⁵ See report by Sibbald B., "Rofecoxib (Vioxx) Voluntarily Withdrawn from Market", 171 *Canadian Medical Association Journal*, 2004, doi: 10.1503/cmaj.1041606.

⁴²⁶ Gilhooley M., "Vioxx's History", p. 950, reporting the testimony of Merck's CEO Raymond Gilmartin at the *Hearing Before the Senate Finance Committee*.

⁴²⁷ Pharmacovigilance in order to fulfil its supervisory role is bound to rely on voluntary post-marketing studies as well as ADR complaints by physicians and consumers. Not every possible side effect can be specifically tested in mandatory post-marketing trials required by the authorising agency. It is however surprising that 1) a theoretical look was deemed insufficient to trigger such type of trial, and 2) when the first data emerged on actual cardiovascular risks a mandatory trial was still not demanded.

above. The post-marketing surveillance only identified it as a collateral result of voluntary post-marketing studies oriented at increasing the product's marketability.

Second, had it not been for said voluntary studies, it is unclear how and when the safety issues related to Vioxx would have been discovered. Let us consider the parallel history of Vioxx's competitor, Pfizer's Celebrex. Celebrex, unlike Vioxx, had not been the subject of long-term studies after approval.⁴²⁸ Interestingly, while the very reason for the existence of the COX-2 inhibitors class of medicines was their gastrointestinal comparative benefit as against other classes of anti-arthritis drugs, no study had been conducted to demonstrate the existence and extent of such a benefit as regards Celebrex.⁴²⁹ As a result of the APPROVe study, now all COX-2 inhibitors including Celebrex include extensive warnings for cardiovascular ADRs in their labelling, and the range of cases and patients they can be prescribed to has been significantly limited.⁴³⁰ While the use of the information resulting from APPROVe has been satisfactory from a safety perspective, it is how the data emerged that raises concerns. If the regulatory scheme relies on voluntary post-marketing studies to uncover potential harm, the question is what would happen should manufacturers within the same class of medicines all act as Pfizer did (that is without further post-approval long-term investigations). The question is far from being irrelevant as the numbers in the pharmaceutical industry tend to be small.⁴³¹ In this case for instance, the competitors were two (Merck and Pfizer), with two alternative products (Vioxx and Celebrex). The potential for both limiting themselves to a first approval with no immediate further investigations was (and is in other cases) a realistic possibility.

⁴²⁸ As can be verified researching 'Celebrex' in the FDA drugs database, available at <http://www.fda.gov/Drugs/default.htm>, and 'Celecoxib' in the EMA database at <http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/>.

⁴²⁹ This has been the object of controversy since the very purpose of COX-2 inhibitors was, as recalled several times, to provide a comparative benefit in terms of gastrointestinal safety. The absence of substantial proof of said benefit in the 'Drug Approval Package', available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20998.cfm, combined with the failure to voluntarily undertake long-term studies, are further unresolved questions of the COX-2 saga.

⁴³⁰ As per the post-2004 modifications to the Celebrex label, retrievable from the FDA database at <http://www.fda.gov/Drugs/default.htm>. Note that *Celecoxib* has been voluntarily withdrawn by Pfizer from the European market: see the relevant European Public Assessment Report, available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR-Summary_for_the_public/human/000466/WC500044631.pdf.

⁴³¹ As discussed in chapters I and III.

The third point, which will be further analysed in the third section, relates to the existence of safer alternatives already in the market. *Naproxen*, while known to potentially cause stomach bleeding, is also a comparatively very safe drug from a cardiovascular perspective. The extent and nature of the harm makes it in general a safer alternative to the strong COX-2 inhibitors.⁴³² It is rather difficult to understand why comparative trials are still very much absent from our regulatory schemes and only undertaken on a voluntary basis by manufacturers to demonstrate marketable comparative benefits.⁴³³

This section focused on a specific case to suggest how risk discovery can be accidental (or randomised as per the section's title). It suggests a struggle of pre- and post-marketing regulatory mechanisms to capture and address safety issues. Section 3 will analyse general figures on ADRs which suggest that this is not an isolated case (although others might not share the same magnitude,⁴³⁴ they occur within the same system and therefore the same structural shortcomings).

It is not the intent of this chapter to argue that regulation should achieve an impossible 'no-risk' utopia. As suggested throughout this thesis, and as will be further discussed in the next chapters focused on the judiciary, pharmaceuticals by nature can be unavoidably unsafe and yet beneficial on balance, or the undiscovered risk they carry may only emerge with time. However, the comparative history of Vioxx and Celebrex does suggest the existence of a component of fortuity in risk discovery that goes beyond the unsurpassable limit of a proper 'development risk'.⁴³⁵ This raises legitimate concerns in the assessment of the output of regulatory schemes, an output the quality of which is crucial both *per se* and as a legitimating element. As recalled above, the Vioxx crisis led to the adoption of regulatory reforms both in the US and in the EU. The nature of these

⁴³² Bombardier C. et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen", p.10526.

⁴³³ The issue of placebo versus marketed competitor test is an uneasy and long-lasting one. We refer here to the discussion *supra* in chapters I, II, and III.

⁴³⁴ The rather unprecedented drumbeat surrounding the Vioxx case is due to the fact that "Rofecoxib was one of the most widely used drugs ever to be withdrawn from the market. In the year before withdrawal it had sales revenue of €2.3 billion": Commission of the European Communities, *Impact Assessment*, 10 December 2008, SEC(2008) 2670, vol I, p. 13. It is important to note that the *Impact Assessment* uses *Rofecoxib* as a pilot case to demonstrate a much more diffuse phenomenon, see the discussion *infra* in section 3.

⁴³⁵ The issue of 'development risk' will be expanded and discussed in chapters VI and VII when analysing the rules of product liability applicable to pharmaceutical products. Generally, a development risk is one that cannot be foreseen given the state of 'technological and scientific knowledge' (the precise definition of which has triggered significant controversy, as will be discussed).

reforms and their impact will be discussed in the concluding section 3 of this chapter.

2. Avandia - Delays in risk communication and safer alternatives?

There is a further lesson to be learned from the Vioxx case, and that is the reaction time of the post-marketing surveillance mechanisms. As suggested above, while a generic and insufficiently investigated ‘theoretical risk’ of cardiovascular ADRs was already known to the manufacturer at the time of approval,⁴³⁶ it took three years for the FDA to introduce an arguably mild and understated ‘Precaution’ section in Vioxx’s label. Once the APPROVe study showed a statistically significant increase in cardiovascular ADRs for consumption of 25mg doses, it was Merck itself that took the initiative and voluntarily withdrew the product. It is almost as if the post-marketing regulatory machinery participated as a spectator. While Vioxx is definitely the most famous drug case of recent times, one would be mistaken to treat it as isolated. The issue this section is concerned with is the reactivity of pharmacovigilance systems to the emergence of newly discovered ADRs. The pilot case we will consider is that of *Rosiglitazone* (commercially distributed by GlaxoSmithKline – GSK – as Avandia).⁴³⁷ The product was first approved by the FDA in May 1999, and subsequently in the EU in July 2000 (after initial rejection in October 1999).⁴³⁸

An analysis of the Avandia case reveals that questions were raised from the very beginning regarding the reliability of the datapool. Ever since its first approval in 1999 by the FDA, drug reviewers expressed concerns about potential severe ADRs including, *inter alia*, myocardial ischaemia.⁴³⁹ The drug was developed to be a step forward compared to

⁴³⁶ As per the testimonies included in the already mentioned Excerpts from Primary Review of NDA 21-042 Osteoarthritis 9 (1999), available at http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_05_F-FDA-Tab-D-1.pdf.

⁴³⁷ See the FDA Approval Letter for application 021071, retrievable from the ‘Approval Package’, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21071_Avandia.cfm, and the EMA approval EMEA/H/C/268 and EMA/230001/2010, available in the EPAR from www.ema.europa.eu.

⁴³⁸ On the initial rejection see the report by Cohen D., “Rosiglitazone: what went wrong?”, *British Medical Journal* 341, 2010: the rejection is known in the literature but no access to primary sources has been possible.

⁴³⁹ As reported in the medical reviews of Avandia’s application: CDER Application N. 021071, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21071_Avandia_medr.pdf; and see Nissen S.E., Wolski K., “Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes”, *New England Journal of Medicine* 356, 2007.

the previous drugs of the Glitazone class marketed at the time (namely *Troglitazone*), which were known for “rare but potentially fatal hepatotoxicity”.⁴⁴⁰ This alleged significant comparative benefit prompted consistent and pressing lobbying by influential stakeholders such as the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).⁴⁴¹ Whether there was an actual need for this new treatment is a controversial issue that will be discussed below. While the FDA authorised the drug immediately after the agency’s dedicated advisory panel recommended approval⁴⁴² (largely based on the absence of hepatotoxicity data, and despite the above-mentioned concerns), the EMA was unsatisfied by the datapool and in particular stressed the need for a long-term study to determine the cardiovascular safety of the drug.⁴⁴³ The lack of evidence from long-term clinical trials and the resulting paucity of available short-term evidence prompted a rejection in October 1999.

The initial decision and its motivations make it rather difficult to grasp why, less than a year later, the EMA decided to reverse its initial decision and approve Avandia for the EU market despite a lack of any new evidence to support this change of view.⁴⁴⁴ It is beyond the scope of this study to analyse the impact of industry’s lobbying on specific approval procedures,⁴⁴⁵ although evidence suggests that a significant amount of pressure was placed on the regulators to have the drug approved.⁴⁴⁶ While this is certainly a concerning scenario that questions the independence of regulators and their decisions,⁴⁴⁷ it is quite interesting to look at the conditions laid down for the approval (interesting for the purposes of this section, uncovering the delays in risk communication and reaction provided by the regulatory system). When the EMA approved Avandia through the centralised procedure for marketing in the EU, the decision was based on an appeal from

⁴⁴⁰ See *Troglitazone* warnings retrievable from the label in the ‘Drug Approval Package’, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20720S12S14_Rezulim.cfm.

⁴⁴¹ See Cohen D., “Rosiglitazone”, reporting strong pressure exercised by the EASD to promote Avandia as a first-line treatment, and the ADA launching a vibrant campaign, both in 1999.

⁴⁴² Nissen S.E., “The Rise and Fall of Rosiglitazone”, *European Heart Journal* 31, 2010.

⁴⁴³ Grattini S., Bertele V., “Rosiglitazone and the Need for a New Drug Safety Agency”, *British Medical Journal* 341, 2010: Grattini was a member of the EMA panel that rejected Avandia’s MAA in 1999.

⁴⁴⁴ As reported in Blind E. et al., “Rosiglitazone: A European regulatory perspective”, *Diabetologia* 54, 2011.

⁴⁴⁵ We have rather focused in chapter IV on the structural imbalance of the regulatory architecture allowing the industry to directly negotiate standards and procedural requirements as peers with the regulators.

⁴⁴⁶ As extensively reported by Cohen D., “Rosiglitazone”, and Pouwels K., van Grootheest K., “The Rosiglitazone decision process at FDA and EMA. What should we learn?”, *International Journal of Risk & Safety in Medicine* 24, 2012.

⁴⁴⁷ See the general literature on ‘regulatory capture’ cited in chapter I.

GSK to reverse the original assessment.⁴⁴⁸ The CHMP, to overcome the obstacles posed by the weak supportive evidence offered by the manufacturer in its initial MAA, evaluated the need for further trials and decided that the approval would be subject to the launch of two post-marketing studies. In particular, one of these studies was a six-year ‘open label’ trial⁴⁴⁹ to investigate the outcomes of cardiovascular hospitalisation and mortality linked to Avandia – the RECORD trial.⁴⁵⁰ Several critics raised their voices to point out the scientific inadequacy of this trial to thoroughly investigate cardiovascular ADRs.⁴⁵¹ It was said that the non-blinded nature of the trial, its low-event rate in a high-risk population, and a non-specific protocol design⁴⁵² were all decisive factors in the substantial failure of the study – which did not reveal in its six-year term any statistically significant difference in the rates of cardiovascular hospitalisation or death resulting from Avandia-based treatments, a finding disproved in 2007 as discussed below. Avandia was therefore approved in the EU with a warning on the risk of heart failure in patients with type-2 diabetes and chronic cardiovascular conditions⁴⁵³ and with the requirement of undertaking the RECORD trial, but, as suggested, no new evidence was provided in support of the immediate reversal of the original rejection.

Avandia quickly became a worldwide best-selling product (a sort of anti-diabetes version of Vioxx),⁴⁵⁴ and by 2004 a WHO investigation signalled that, with the ever-growing consumption of the drug, evidence of cardiovascular ADRs was emerging and steadily increasing.⁴⁵⁵ It was however only in 2006 that both the EMA and the FDA

⁴⁴⁸ Pouwels K., van Grootheest K., “The Rosiglitazone decision process at FDA and EMA”.

⁴⁴⁹ That is a typology of clinical trial in which both the patients and the researchers are aware of which treatment is being administered: a ‘non-blinded’ trial as opposed to the typical randomised double-blind clinical trials discussed in chapters I, II and III.

⁴⁵⁰ Acronym for Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes. Results are available at <https://clinicaltrials.gov/ct2/show/NCT00379769>.

⁴⁵¹ Pocock P.D. et al., “Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicenter, randomized open-label trial”, *The Lancet* 373, 2009.

⁴⁵² See report in DHHS, “Committee on NDA 21071”, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM218493.pdf>.

⁴⁵³ See EMA Assessment Report doc ref EMA/73099/2015, available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001027/WC500181904.pdf.

⁴⁵⁴ Figures from various journalistic sources confirm that Avandia was making around \$3 billion a year worldwide: see Cohen D., “Rosiglitazone”.

⁴⁵⁵ Pouwels K., van Grootheest K., “The Rosiglitazone decision process at FDA and EMA”. Personal communications with the GSK R&D department confirm, albeit informally, the reception of alerts from WHO.

reacted with the approval of new warnings of potential cardiovascular events.⁴⁵⁶ This two-year gap between information made available by the WHO and the adoption of reactive measures calls into question the effectiveness of the post-marketing surveillance regime. In particular, what emerges is that there is a gap between reporting duties, assessment of emerging data, and consequent reactive measures.⁴⁵⁷ As the next section will discuss, this gap has been largely imputed to an inadequate and at times confusing legislative framework where roles and responsibilities of industry and regulators were (and possibly still are) allegedly unclearly identified.⁴⁵⁸

The most significant step forward in identifying the reality of cardiovascular risks related to Avandia consumption emerged in 2007. A group of scientists concerned by the cardiovascular safety of Glitazone class drugs undertook a meta-analysis⁴⁵⁹ of data emerging from Avandia trials and published it in the *New England Journal of Medicine* (*NEJM*).⁴⁶⁰ The study for the first time showed the existence of a “significant increase in myocardial infarction” associated with *Rosiglitazone* as compared to placebo or alternative marketed treatments.⁴⁶¹ The conclusions of the study triggered a reaction from the FDA, which undertook an independent study the results of which suggested a statistically significant increase in cardiovascular events of 40%.⁴⁶² It is now essential to underline a fundamental fact in this reconstruction. The meta-analysis conducted by the *NEJM* scientists was initially impeded by GSK, which refused to disclose clinical data based on the usual Confidential Business Information (CBI) exception.⁴⁶³ However, in 2004 GSK had settled a case in the state of New York in a lawsuit involving failure to disclose the

⁴⁵⁶ See the evolution in the 2006 label in the FDA ‘Drug Approval Package’, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21071_Avandia.cfm, and in the EMA EPAR, available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000268/WC500029110.pdf

⁴⁵⁷ See the Commission of the European Communities, *Impact Assessment*, 10 December 2008, SEC(2008) 2670, vol I, p. 13.

⁴⁵⁸ *Ibidem*.

⁴⁵⁹ A meta-analysis is a second take on previously conducted trials – it uses statistical methods to identify patterns, discrepancies and other statistically significant relationships emerging from multiple studies. As such, it is considered the most thorough statistical source of data.

⁴⁶⁰ Nissen S.E., Wolski K., “Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes”, *New England Journal of Medicine* 356, 2007.

⁴⁶¹ *Ibidem*.

⁴⁶² FDA, “Briefing Document Division of Metabolism and Endocrine Products and Office of Surveillance and Epidemiology”, July 2007, available at <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-02-fda-backgrounder.pdf>

⁴⁶³ As reported by one of the *NEJM* authors, Nissen S.E., “The Rise and Fall of Rosiglitazone”. See in general the discussion in the opening sections of chapter III.

results of unfavourable studies related to an increased suicide rate in children and adolescents treated with *Paroxetine* (commercialised by GSK under several brand names, the most common one being Paxil). The terms of the settlement required GSK to disclose all clinical trials conducted by GSK after December 2000,⁴⁶⁴ which allowed the *NEJM* group to undertake the meta-analysis, relying on 42 randomised trials of which 35 had not been published.⁴⁶⁵ Note that whereas trials data between December 2000 and April 2007 (when the *NEJM* group accessed the data) was available, previous trials (including the pivotal ones leading to the initial marketing authorisation) are still protected as discussed in chapter III.

The *NEJM* study (based on data made accessible by a court case) was a turning point in the Avandia saga. Both the FDA and the EMA initially reacted with a further modification of the labelling, introducing renewed warnings to patients for potential cardiovascular ADRs.⁴⁶⁶ Based on the final results of the RECORD trial, published in *the Lancet* in June 2009,⁴⁶⁷ both agencies decided to keep the medicine in the market as the study showed no significant statistical increase in cardiovascular hospitalisation and death.⁴⁶⁸ However the strong critiques of the study's design, revolving around its unfitness to effectively achieve its purported goal, weakened its reliability. In July 2010 an FDA advisory committee severely criticised the findings of the RECORD trial and recommended a withdrawal of the product or a significant restriction of its use.⁴⁶⁹ The agency opted for the latter solution. Meanwhile, the EMA reached a more definitive conclusion in September 2010, recommending a suspension of the marketing authorisation on the grounds that the risks of cardiovascular ADRs outweighed the drug's

⁴⁶⁴ An analysis of the case and the settlement is provided in chapter VII.

⁴⁶⁵ Nissen S.E., "The Rise and Fall of Rosiglitazone": see the open access trial database provided by GSK as a result of the 2004 settlement at <http://www.gsk-clinicalstudyregister.com/>.

⁴⁶⁶ See again the 2007 version of the labels in the FDA 'Drug Approval Package', available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/21071_Avandia.cfm, introducing a so called 'black box' warning against cardiovascular ADRs, and similarly in the EMA EPAR at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000268/WC500029110.pdf.

⁴⁶⁷ Home P. et al., "Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type-2 diabetes (RECORD): a multicenter randomized, open-label trial", *the Lancet* 373, 2009.

⁴⁶⁸ *Ibidem*, see 'findings'.

⁴⁶⁹ See Cohen D., "Rosiglitazone", and FDA, "Drug Safety Communication: Ongoing review of Avandia (rosiglitazone) and cardiovascular safety", available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm201418.htm#sa>.

benefit, in particular due to the presence of safer alternatives in the market.⁴⁷⁰

As for the Vioxx saga, there are at least three lessons we can learn from the Avandia case. The first and most striking one relates to prolonged delays in risk communication and consequent reactive regulatory measures. Concerns over cardiovascular risks were present from the beginning, but the proposed regulatory solution was, at first, a requirement for an inadequately designed post-marketing study. More to the point, when concerns about cardiovascular events linked to Avandia were finally raised by the WHO in 2004, the regulatory response to the issue took two years, with modified warnings approved in 2006. Subsequently, when in 2007 the *NEJM* study offered a meta-analysis showing a 30% to 40% increase in risks of cardiovascular ADRs (confirmed to be 40% by the following FDA review), both the EMA and the FDA took three years to take corrective measures, eventually significantly restricting the use of the drug in the US and suspending its marketing authorisation in the EU.⁴⁷¹

The second point, not dissimilar to what has been already suggested for Vioxx, is the presence of safer alternatives in the market, which in turn calls into question the necessity of approval in the first place. In particular, the hepatotoxicity advantage achieved by Avandia as compared to previous anti-diabetes treatments proved to be far less beneficial than the increased risk factor for cardiovascular events.⁴⁷² In other words, it appears from this reconstruction and the studies it relies upon that the regulatory system (in both the US and the EU) allows approval of under-investigated new products as treatments for conditions already widely covered by effective marketed competitors.⁴⁷³

The third element, which will be further expanded in chapter VII, is related to the availability of what we have referred to in previous chapters as ‘relevant scientific knowledge’. The *NEJM* study which uncovered statistically significant risks linked to Avandia was only made possible by the result of a court case imposing full disclosure obligations (albeit for a limited period of time) on GSK. The obvious related question

⁴⁷⁰ See EMA, “Recommendation for suspension of Avandia Marketing Authorisation”, Doc. Ref. EMA/585784/2010, available at http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/09/WC500096996.pdf

⁴⁷¹ *De facto* reverting back to the original decision of 1999 when the MAA was rejected for lack of safety evidence.

⁴⁷² Nissen S.E., Wolski K., “Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes”.

⁴⁷³ Grattini S., Bertele V., “Rosiglitazone and the Need for a New Drug Safety Agency”.

being *quid* when no exogenous element intervenes to impose data availability?

3. Uncertainty ex ante, insufficiency ex post?

The events of the 2000s, with significant pharmaceutical product-related cases questioning the ability of the regulatory system to deliver effective and safe medicines, prompted the adoption of reforms very much focused on post-marketing surveillance roles and the responsibility of industry and regulators. The cases analysed in the previous sections uncovered a series of issues, foremost among which include the fortuity of risk discovery beyond the systemic uncertainties of the scientific process, and long delays in risk communication and reactive measures. In the midst of these fundamental regulatory issues lies the policy problem that new drugs are often not needed, as comparatively safer alternatives are already marketed. This section analyses these matters through the lens of the regulatory reforms adopted by the US and the EU between 2007 and 2012, and attempts a critical conclusion on the safety output provided by the regulatory systems alone.

In the aftermath of the Vioxx crisis the FDA faced severe criticism for inadequacy in the delivery of safe and effective medicines. The unfolding of events questioned the reliability of both pre- and post-marketing regulatory measures. However, noting that pre-marketing testing is characterised by inherent limitations which could “not be changed without adding considerably to the time and expense of drug approvals, which would delay patient access to potentially beneficial drugs”⁴⁷⁴ (in deference to the pro-marketing attitude that emerged as a result of the ‘drug lag’ described in chapter II), the FDA pressured Congress to gain greater post-marketing surveillance powers, in the specific form of increased autonomy to require further clinical trials to face emerging safety concerns.⁴⁷⁵ Until 2007, the pharmacovigilance system was considered adequate to catch rare ADRs mostly unrelated to the prescription use of the products (what are commonly referred to as ‘signature damages’), but its shortcomings emerged in its substantial inability to effectively uncover the marketed medicine’s contribution to common ADRs (the most common kind of drug-related damage: not a signature one, but an increase in the

⁴⁷⁴ IOM Report, *The Future of Drug Safety – Promoting and Protecting the Health of the Public*, 2006, p. 38.

⁴⁷⁵ Gilhooley M., “Vioxx’s History”, p. 956 ff.

probability of a certain type of ADR).⁴⁷⁶ In this sense, in the case of both Vioxx and Avandia, the limits of the pharmacovigilance system emerged quite dramatically. Another line of criticism identified the potential for a conflict of interest between the pre- and post-marketing activities of the FDA. Specifically, the argument suggests that since the division charged with approval of new products (the FDA's Office of New Drugs) is the same division vested with post-marketing surveillance authority, this double role might very well cause an internal conflict of interest to the detriment of accurate and effectively conducted pharmacovigilance,⁴⁷⁷ as the same office would be reluctant to contradict its earlier findings. While this latter criticism has yet to be legislatively addressed, Congress reacted to the former with the adoption of the FDAA of 2007⁴⁷⁸ - the scope of the Act is wider, but there is a specific focus on an expansion of the FDA's post-approval authority, especially as regards post-approval testing or warning requirements.

Under the FDAA, the agency has the authority to require a manufacturer to undertake a post-approval clinical trial to ascertain the existence of previously undiscovered or under-reported ADRs, based on appropriate scientific data.⁴⁷⁹ While this is certainly a step forward from a scenario dependent on voluntary initiatives of marketing authorisation holders, it is unclear to what extent the Vioxx case would have benefitted from the new provision since for approved products the requirement can only be imposed on the basis of new safety information⁴⁸⁰ – in other words the 'theoretical' risk identified for Vioxx would not have sufficed, and only after the VIGOR trial could a formal requirement have been imposed. In response to the delays in introducing proper warnings, the FDAA also reinforced the FDA's authority to require modifications to the safety labelling of marketed products,⁴⁸¹ reducing the pure negotiating space that substantially delayed and watered down the labelling changes for Vioxx. This authority is however subject to a dispute resolution mechanism which is dealt with on a case-by-case basis by the agency following a general blueprint (the legislation leaves ample margins of manoeuvre to the agency in the determination of specific procedures) – which provides that disputes over the modification of product labelling should be determined through the

⁴⁷⁶ See IOM Report, *The Future of Drug Safety*.

⁴⁷⁷ Carpenter D., *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA*, Princeton University Press, 2010, p. 630.

⁴⁷⁸ Food and Drug Administration Amendments Act, 2007, P.L. 110-85, 110 Stat.

⁴⁷⁹ *Ibidem*, section 901(a), 355(o)(3)(A).

⁴⁸⁰ *Ibidem*, section 901(a), 355(o)(3)(C).

⁴⁸¹ *Ibidem*, section 901(a), 355(o)(4)(F).

adoption of a regulation containing a proposed ruling and sufficient time for comments by the counterparty.⁴⁸² To ensure adequate enforcement of these new mechanisms, the FDAA gives the agency authority to impose substantial fines for violations of required measures – the fines can go up to a quarter of a million dollars for any single violation, to be doubled after 30 days of protracted violation.⁴⁸³

The 2007 FDAA with the introduction of fines attempted to tackle another essential issue affecting the effectiveness of post-marketing surveillance: the scarcity of financial resources, arguably one of the major factors responsible for the inability of the agency to promptly react to emerging ADRs.⁴⁸⁴ The principal source of revenue for the agency to reinvest in safety and efficacy monitoring is the mechanism contained in the Prescription Drug User Fee Act (PDUFA) described in chapter II. In 2012, with the adoption of the Food and Drug Administration Safety and Innovation Act (FDSIA), PDUFA was re-authorised for the fifth time since its first adoption in 1992.⁴⁸⁵ While PDUFA V integrates a series of new provisions very much focused on risk communication mechanisms,⁴⁸⁶ the financing mechanism based on manufacturers' fees for NDAs is maintained. Since its first adoption, the PDUFA mechanism has produced an undeniably significant income and become the major financial resource for the agency's monitoring duties, but its limits in covering the costs of post-marketing surveillance tasks are reported in several FDA studies, such as the 2013 evaluation of the PDUFA Workload Adjuster,⁴⁸⁷ and the 2008 "Post-marketing Commitments Study Final Report".⁴⁸⁸ While certainly introducing much-needed improvements to the post-marketing surveillance mechanisms, the 2007 legislation is not without its critics. Particularly, the concern is that the scope of the intervention is still insufficient to systematise FDA's monitoring duties

⁴⁸² *Ibidem*.

⁴⁸³ *Ibidem*, section 902(b), 333(4)(A).

⁴⁸⁴ The literature is vast on the subject: see IOM Report, *The Future of Drug Safety – Promoting and Protecting the Health of the Public*; Struve C.T., "The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation", *Yale Journal of Health Policy, Law & Ethics*, 2005; and the Supreme Court case *Wyeth v. Levine*, 129 S. Ct. 1187, 2009, discussed in chapters VI and VII.

⁴⁸⁵ Food and Drug Administration Safety and Innovation Act, 2012, P.L. 112-144, 126 Stat.

⁴⁸⁶ See PDUFA V Implementation for Fiscal Years 2013-2017, available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

⁴⁸⁷ FDA, "An Evaluation of the Prescription Drug User Fee Act (PDUFA) Workload Adjuster", April 2013, available at <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM350567.pdf>.

⁴⁸⁸ FDA, "Postmarketing Commitments Study Final Report", January 2008, available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119856.htm>.

over marketed medicines' life cycles as the funding mechanism through user fees provides insufficient resources.⁴⁸⁹ This concluding observation on the limited financial resources dedicated to the pharmacovigilance system constitutes an appropriate *trait d'union* to discuss the regulatory reforms adopted in Europe between 2010 and 2012.

Similarly to the US scenario, the European legislation governing post-marketing surveillance has been subject to abundant criticism in the wake of the pharmaceutical cases of the mid and late 2000s. Originally laid down in recalled Directive 2001/83 and Regulation 726/2004,⁴⁹⁰ the pharmacovigilance system was subject to extensive revision, first in 2010 with the adoption of Regulation 1235/2010 and Directive 2010/84,⁴⁹¹ and finally in 2012 with the adoption of Directive 2012/26.⁴⁹² The reasons for this legislative intervention were identified by the EMA in a 2008 Impact Assessment presented by the Commission to the European Parliament.⁴⁹³ The assessment underlines how despite pre-marketing approval procedures and requirements (which are in any event never expected to provide a risk-free result), ADRs are “the fifth most common cause of death and are responsible for 3-10% of all admissions to hospitals in the EU”.⁴⁹⁴ The report extensively describes the effects of the shortcomings in the EU post-marketing surveillance regime, with a series of estimates reported below:⁴⁹⁵

- 0.12% – 0.22% of hospital admissions result in death due to an ADR, corresponding to 100,800 - 197,000 deaths annually in the EU.
- 3 – 10 % of hospital admissions are caused by ADRs corresponding to 2.5 – 8.4 million annually in the EU.
- 2.1 – 6.5% of hospitalised patients suffer an ADR, corresponding to 1.8 – 5.5 million annually in the EU.
- ADR-related costs other than those caused by hospitalization are estimated at € 63.2

⁴⁸⁹ IOM Report, *Ethical and Scientific Issues in Studying the Safety of Approved Drugs*, 2012.

⁴⁹⁰ See section 2 of chapter II.

⁴⁹¹ Regulation (EU) 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004, OJ 2010 L 348/1; Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC, OJ 2010 L348/74.

⁴⁹² Directive 2012/26 of the European Parliament and of the Council of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance, OJ 2012 L299/1.

⁴⁹³ Commission of the European Communities, “Impact Assessment”, 10 December 2008, SEC(2008) 2670, vol I, available at http://ec.europa.eu/health/files/pharmacos/pharmpack_12_2008/pharmacovigilance-ia-vol1_en.pdf.

⁴⁹⁴ *Ibidem*, p. 9.

⁴⁹⁵ *Ibidem*, p. 12.

billion annually in the EU.

- € 79 billion represents a reasonable estimate of the total societal cost of ADRs occurring in the EU.

In analysing the reasons for this less than optimal scenario, the EMA recognised that the original framework for the post-marketing surveillance mechanism contained in the pre-2010 legislation was out-dated, as it was still very much modelled on the scheme adopted in the 1960s and subsequently amended (but never restructured) in 2001 and 2004.⁴⁹⁶ This failure to properly update and modernise the system is therefore identified as the main cause of its weaknesses, which are grouped in a series of major categories.

First, the out-dated system did not provide a clear division of roles and responsibilities between the central regulator (EMA), MS authorities, and marketing authorisation holders, which resulted in delays in risk communication as well as low levels of post-marketing compliance.⁴⁹⁷

Second, the shortcomings of the decentralised marketing authorisation procedure emerged in this field (as well as in the pre-marketing one discussed in chapter II), slowing down the European level of decision-making in addressing ADRs. Because legal provisions on referrals of emerging risk were unclear they were rarely used, with consequent divergent and incoherent actions taken at MS level.⁴⁹⁸

Further, the reporting rules proved to lack proactivity on the side of the EMA. For instance the fact that post-marketing requirements were simply described, not conducted by the authority, rendered compliance difficult to achieve (in the Avandia case, the inability of the EMA to conduct the RECORD trial itself was a prominent factor in its substantial failure).⁴⁹⁹ Moreover, there was a recognition that post-marketing studies, being

⁴⁹⁶ *Ibidem*, p. 12: “The 2001-Review did not include a systematic review of the EU pharmacovigilance rules and did not assess their effectiveness” – noting subsequently, pp. 13-14, the permanence of disharmony in pharmacovigilance rules and requirements.

⁴⁹⁷ *Ibidem*, p. 15. Notably, a similar conclusion is restated in EMA, “One-year report on human medicines pharmacovigilance tasks of the European Medicines Agency”, Doc Ref EMA/171322/2014, available at http://ec.europa.eu/health/files/pharmacovigilance/2014_ema_oneyear_pharmacov_en.pdf.

⁴⁹⁸ Commission of the European Communities, “Impact Assessment”, p. 16: this lack of coherence seems to be improving with the new legislation, as reported in EMA, “One-year report on human medicines pharmacovigilance”.

⁴⁹⁹ Commission of the European Communities, “Impact Assessment”, p. 17, and on the shortcomings of the RECORD trial see the discussion *infra*.

substantially left to the initiative of the manufacturers, were “frequently conducted for promotional rather than safety reasons”,⁵⁰⁰ providing only poor quality data (as for instance in the Vioxx case, the VIGOR study was designed for the sole purpose of identifying a comparative advantage as against its direct competitor).

In light of these observations, the EU reacted with the above-mentioned legislation in 2010 and 2012. The choices made are not dissimilar from what we have already observed in the US. One of the most significant changes is a stronger role for the EMA in requiring and supervising post-marketing studies to assess specific safety concerns.⁵⁰¹ Based on the Vioxx experience, which highlighted that it is not only highly innovative biotechnological products that carry the risk of widespread and possibly fatal ADRs, the new legislation extends the scope of application of Risk Management Plans (RMPs, a post-authorisation road-map for complementary testing and monitoring duties to guarantee a “prospective safety evaluation of products”, originally limited to a restricted list of innovative products) to all new MAAs if required.⁵⁰²

The proactive risk management conducted by the EMA under the new legislation is to be considered an positive step in providing better quality data on the one hand, and simplifying the convoluted and unclear partition of roles and responsibilities of the previous legislation. However, while the more central role of the EMA has certainly had the merit of rationalising an otherwise disharmonious legislative field, similarly to what has been said about the FDA, a crucial residual concern revolves around the lack of financial resources. Before the adoption of the 2010-2012 legislation the lack of funding to guarantee effective post-marketing monitoring was a generally recognised phenomenon. The issue with the recent reforms is that they do not introduce any increase in resources for the implementation of their new provisions.⁵⁰³ The idea is that simplification should

⁵⁰⁰ *Ibidem*, p. 17.

⁵⁰¹ See in particular art. 1(4) inserting a new art. 10a in Regulation 726/2004 providing that: “1. After the granting of a marketing authorisation, the Agency may impose an obligation on the marketing authorisation holder: (a) to conduct a post-authorisation safety study if there are concerns about the risks of an authorised medicinal product [...]”.

⁵⁰² See the new arts. 104(3) and 104a(2) of Directive 2001/83, and EMA, ‘Guidelines on good pharmacovigilance practices (GVP)’, Doc Ref EMA/838713/2011 Rev 1*, 2014, available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129134.pdf.

⁵⁰³ The new legislation introduces a mechanism similar to the one provided by the American PDUFA – see the discussion *infra*. For an extended criticism of the failure to provide EMA with new financial resources in spite of a greater centrality of its role, see Grattini S., Bertele V., “Anything new in EU pharmacovigilance?”, *European Journal of Clinical Pharmacology* 67, 2011.

guarantee a significant decrease in expenses, saving essential resources to be fruitfully reinvested in the conduction of post-marketing duties. However, the scope of the reform, and in particular the extension of RMPs to all product applications, could prove a serious obstacle to the achievement of the legislative goals. Similarly to the American PDUFA, the 2010 legislation empowers the EMA to charge fees to manufacturers applying for marketing authorisation,⁵⁰⁴ but whether this is sufficient to fund the extensive post-marketing surveillance activities with which the agency is entrusted is unlikely.⁵⁰⁵ Whereas the FDA study on compliance with post-marketing requirements shows that only 30% of post-marketing commitments are fulfilled by manufacturers,⁵⁰⁶ no data is available on fulfilment percentages in the EU, where all that is available is a generic acknowledgment that “frequently post-authorisation safety studies are not conducted or completed”.⁵⁰⁷ Since the legislation has been in force for less than three years (it came into force in July 2012), a few more years will be necessary to appreciate whether the new legislative provisions are fully effective and the financial resources adequate.

We concluded chapter III with a remark that uncertainty seemed to permeate pre-marketing scrutiny because the provenance and reliability of data proved difficult if not impossible to assess. Chapter IV suggested that traditional forms of legitimacy supporting this rather uncertain scenario are fundamentally absent, and that it is therefore only from an analysis of the output of the system that one can extrapolate a legitimization of its rules. In this sense, the conclusion of this chapter is interlocutory. The above description of the safety output suggests that risk discovery is characterised by elements of fortuity that are more the product of imperfect regulatory mechanisms than of unavoidable scientific hazards, while the reaction time of the regulatory system can prove to be lengthy and ineffective. Important reforms have been put into place to face these challenges, but the regulators while legislatively empowered may struggle to find adequate

⁵⁰⁴ See the new art. 67(3) of Regulation 726/2004 as amended by Regulation 1235/2010: “The Agency’s revenue shall consist of a contribution from the Union and fees paid by undertakings for obtaining and maintaining Union marketing authorisations and for other services provided by the Agency, or by the coordination group as regards the fulfilment of its tasks [...]”.

⁵⁰⁵ See the negative evaluation released by the Commission, “Proposal for a Regulation of the European Parliament and the Council on fees payable to the European Medicines Agency for the conduct of pharmacovigilance activities in respect of medicinal products for human use”, COM(2013) 472 final – based on the related Opinion released by DG SANCO, April 2013, available at http://ec.europa.eu/smart-regulation/impact/ia_carried_out/docs/ia_2013/sec_2013_0372_en.pdf.

⁵⁰⁶ FDA, “Postmarketing Commitments Study Final Report”.

⁵⁰⁷ Commission of the European Communities, “Impact Assessment”, p. 17.

resources to fulfil their tasks.

The four chapters dedicated to the institutional design of pharmaceutical regulation paved the way for the argument that the regulatory system cannot be self-sufficient in the pursuit of consumer safety. The following chapters will discuss the potential for courts to constitute the necessary exogenous elements to open up and complement the *closed system* as we described it in the opening chapter.

CHAPTER VI⁵⁰⁸

THE LENS OF THE JUDICIARY IN PHARMACEUTICAL SAFETY

RENEWED ROLES FOR TRADITIONAL RULES?

After analysing the regulatory dimension of pharmaceutical safety and underlining some of its problematic features, the next chapters will be dedicated to the lens of the judiciary in pharmaceutical safety. As the most prominent role of courts in pharmaceutical cases is to adjudicate tort claims in product liability suits, the analysis discusses the development of US and EU product liability rules confronted with pharmaceutical cases. The focus of this chapter is on two specific aspects: foreseeability of risk and compliance with regulatory requirements. The purpose is to create a link between the regulatory mechanisms and court litigation by addressing issues that are of the essence in both sets of rules: their relationship to risk and its assessment. The intent is therefore to set the scene as regards the attitude of liability rules towards risk in pharmaceutical products, because it is within the sphere of tort law that the following chapters will examine to what extent it is possible to rely on courts for the purposes of refining the quality of risk assessments, legitimising the system, and enhancing the delivery of safety.

1. Pharmaceutical products and the law of torts

There is an antique dispute over the liability regime that would best fit pharmaceuticals. The reason for this is easily understandable if we consider the inherent

⁵⁰⁸ This chapter is partially based on a previous work, Rizzi M., “Regulating risks in pharmaceutical law: the need of an optimal interplay between products safety and products liability”, *Opinio Juris in Comparatione*, Vol. 1/2011, Paper No. 2, available at SSRN: <http://ssrn.com/abstract=1857434>, and on the forthcoming Rizzi M., “Non-Measurable Negotiations – The EU between Transnational Regulation of Pharmaceuticals and Private Law”, in Cremona M., Micklitz H.-W., *Private Law in the External Relations of the EU*, Oxford University Press.

risk that characterises these products.⁵⁰⁹ The impossibility of absolute safety poses inevitable questions over the extent to which a producer can be held liable for damages caused by his products. The issue is further complicated by the extensive regulatory oversight established for pharmaceutical products that we have described above, because of the financial and time burdens imposed by such regulations.⁵¹⁰

Whether and how pharmaceuticals should be treated differently from other types of products has “consumed more time and effort than about any other particularized issue of products liability law”.⁵¹¹ There is indeed a paradox that is inherent to medicines, appropriately described by M. Stuart Madden: “as one of the greatest triumphs of the twentieth century, their powerful chemicals and biologics save millions of human beings from suffering and death; yet, these same chemicals also cause great suffering and death”.⁵¹² While all medicines create risks and benefits, and a measure of

⁵⁰⁹ It is interesting for the purpose of defining the unavoidability of risk in pharmaceutical products to recall the definition of “unavoidably unsafe” as provided by *comment k* of Section 402/A of the *Restatement (Second) of Torts*. *Comment k* states: “Unavoidably unsafe products. There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs. An outstanding example is the vaccine for the Pasteur treatment of rabies, which not uncommonly leads to very serious and damaging consequences when it is injected. Since the disease itself invariably leads to a dreadful death, both the marketing and the use of the vaccine are fully justified, notwithstanding the unavoidable high degree of risk which they involve. Such a product, properly prepared and accompanied by proper directions and warnings, is not defective, nor is it *unreasonably* dangerous. The same is true of many other drugs, vaccines, and the like, many of which for this very reason cannot legally be sold except to physicians, or under the prescription of a physician. It is also true in particular of many new or experimental drugs as to which, because of lack of time and opportunity for sufficient medical experience, there can be no assurance of safety, or perhaps even of purity of ingredients, but such experience as there is justifies the marketing and use of the drug notwithstanding a medically recognisable risk. The seller of such products, again with the qualification that they are properly prepared and marketed, and proper warning is given, where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk.”

⁵¹⁰ See the discussion in chapter II, and for an overview of cost issues see Hodges C., *European Regulation of Consumer Product Safety*, p. 48: “The average cost of discovering and developing a new drug is now put at over \$800 million and rising at an annual rate of 7.4% above general price inflation: Boston Consulting Group, *A Revolution in R&D: How Genomics and Genetics are Transforming the Biopharmaceutical Industry*, Boston, 2003; DiMasi J., Hanson R.W., Grabowski G., “The Price of Innovation: New Estimates of Drug Development Costs”, *Journal of Health Economy*, 22, 2003. It is well known that the potential profits can be enormous. It has been commented that the increasing cost of drug development is likely to promote the situation where companies invest only in the development of those new drugs that are expected to yield peak annual sales greater than \$500 million: Rawlins M.D., “Cutting the Costs of Drug Development?”, *Nature*, 3, April 2004.”

⁵¹¹ Henderson J.A., Twerski A.D., “Drug designs are different”, *Yale Law Journal* 151, 2001.

⁵¹² Madden M.S., “The enduring paradox of products liability law relating to prescription pharmaceuticals”, *Pace Law Review* vol. 21, 2000.

hazard is unavoidable,⁵¹³ the question is how to strike the optimal balance between these risks and benefits, and indeed how to adequately identify them in the first place, given that product labelling alone cannot always properly warn consumers of the inherent risks of taking the medicine⁵¹⁴ and therefore cannot be delegated the task of consumer safety.

The impossibility of a perfect regulator makes the issue a pressing one. At a general level, Christopher Hodges among others points out that legislative, budgetary, and political constraints clash with “the ideal of a perfect regulatory body that optimally protects the public from exposure to potentially harmful products”.⁵¹⁵ Specifically, we have analysed in chapter II the process of detachment of technical bodies from the legislative circuit, while chapters III and V have pointed at the structural and budgetary limitations hindering adequate levels of monitoring of clinical trials sites, on the one hand, and the shortcomings of post-marketing surveillance on the other. Hodges’ critiques must then be coupled with the substantial uncertainties and legitimacy issues raised by the transnationalisation of pharmaceutical regulatory procedures as described in chapters III and IV. In this context this thesis takes the position that product liability should be normatively considered an active component of the concept of ‘pharmaceutical safety’, complementing and legitimating regulatory procedures and decisions.⁵¹⁶

Setting aside for the moment the claim regarding their pedagogical potential, there is now a need to give a descriptive *résumé* of tort law attitudes towards risk. The answer is necessarily multi-faceted. There are national experiences where, due to shortcomings occurring in regulatory practices, product liability law has a role to play in compensating persons harmed unnecessarily by defective drugs, in deterring production and sale of unsafe products, and in promoting drug safety, but on the basis of a system of rules which

⁵¹³ It is worth noting that there is a common understanding, especially in US literature, that drug hazard is inherent and simply cannot be removed. While this is true to a certain extent, the hazard in some drugs may be reduced or eliminated by changing the prescribed dosage, the active ingredients in combination drugs, or the inert ingredients used in a drug. A discussion from a legal rather than pharmacological perspective can be found in Green M., “Prescription Drugs, Alternative Designs, and the Restatement (Third): Preliminary Reflections”, 30 *Seton Hall Law Review* 207, 199.

⁵¹⁴ See for example Smith R., “The Vagueness of Informed Consent”, 1 *Individual Health Law Review* 109, 2004.

⁵¹⁵ Hodges C., *European Regulation of Consumer Product Safety*, p. 48. On weaknesses in the regulatory schemes, see for an analysis from the ‘tort law perspective’ Rabin R., “Reassessing Regulatory Compliance”, 88 *Georgetown Law Journal* 2049, 2000.

⁵¹⁶ The idea of complementarity has been recently restated by Goldberg R., *Medicinal Product Liability and Regulation*, Hart Publishing, 2013, see for example pp. 161-162. The analysis, very much centred on the concept of regulation providing minimum standards complemented by tort litigation, will be extensively referred to in the descriptive analysis.

is substantially a negligence one.⁵¹⁷ The United Kingdom provides a valid example of this attitude, as does the European Product Liability Directive as interpreted by the ECJ, which provides, despite a strict wording, a relatively negligence-oriented regime.⁵¹⁸ Other countries on the other hand, such as Spain or Germany, opt for strict liability for harms caused by pharmaceutical products.⁵¹⁹ The United States is characterised by a unique evolution from the strict liability wording of the *Restatement (Second) on Torts* to the current negligence-based *Restatement (Third)*, with a significant intermission. As recalled in the opening chapter, in 2006 the FDA adopted unilaterally the doctrine of preemption for FDA-approved new products, shielding manufacturers compliant with federal regulation from state tort claims. The line of argument adopted by the Supreme Court to overcome this unprecedented attempt to exclude liability claims will be an essential feature of this analysis.

2. The United States approach to pharmaceutical tort litigation

The opening chapter highlighted that a key element of both regulatory and liability assessments is ‘relevant knowledge’. Therefore, the issue of interest here is to identify the attitude of product liability law towards that concept. In the US, the key idea is the one referred to as ‘state of the art’, which is a mutating concept that has never been comprehensively defined, either by courts or by statutes, as suggested by David Owen⁵²⁰ and several other North-American scholars.⁵²¹ More precisely, while state statutes or courts, singularly considered, have a working definition of what is to be considered ‘state of the art’, a uniform federal conception is absent, and the *Restatements on Torts (Second and*

⁵¹⁷ The topic is discussed by Reimann M., “Liability for defective products at the beginning of the twenty-first century: emergence of a worldwide standard?”, *American Journal of Comparative Law*, 2003, and subsequently restated up until the recent work of Goldberg R., *Medicinal Product Liability and Regulation*. The reference to negligence rules in drug litigation will be further explored *infra*.

⁵¹⁸ See below the discussion on the seminal case C-300/95 *Commission of the European Communities v United Kingdom of Great Britain and Northern Ireland* ECR 1997, I-02649.

⁵¹⁹ See below the discussion on the Spanish Ley 22/1994, *Sobre Responsabilidad Civil Por Danos Causados por Productos Defectuosos* and the German *Gesetz über den Verkehr mit Arzneimitteln (Arzneimittelgesetz - AMG)*, of 24 August 1976.

⁵²⁰ Owen D., *Products liability law (2nd ed.)*, Hornbook Series, Thomson West Group, 2008, pp. 675-681; Owen D., Montgomery J., Davis M.J., *Products Liability and Safety*, Foundation Press, 2014.

⁵²¹ For example Henderson J.A., Twerski A.D., *Products liability – problems and process*, 5th ed., ASPEN Publishers, 2004; and a recent confirmation by Goldberg R., *Medicinal Product Liability*, p. 69.

Third) have steered clear of the issue. There are several causes that may explain this phenomenon. The simplest is to look at the problem from a semantic point of view. ‘State of the art’ is an incomplete phrase: you need to know about which particular ‘art’ you are referring to in a particular situation. In other words the question is: state of the art *of what?* The answer varies from state to state, being considered in some cases as the most up-to-date scientific knowledge, in others as the industrial customary practice.⁵²²

To summarise, in American product liability law, ‘state of the art’ is an unrefined concept whose meaning and proper role are in continuous evolution. In the impressive variety of definitions and interpretations of such a phrase, it is possible to identify a thin common theme emerging from the cases and the statutes: “reluctance to impose liability on manufacturers for dangers that were unknowable, or unpreventable, at the time their products were sold: reluctance to hold producers responsible for risks they cannot control”.⁵²³ This common theme has led to a theoretical mutation of the idea of ‘state of the art’ from *Restatement (Second)* to *Restatement (Third)*, which is interesting and potentially helpful to understand the further evolution of the legal regime of pharmaceutical product safety in the US. The *Restatement (Second)* imposed a strict liability regime for damages caused by defective products, adopting the so called “consumer expectation test” to evaluate the safety of the products.⁵²⁴ To attenuate the potentially excessive harshness of the rule, the American Law Institute (ALI) introduced *comment j* to section 402A, regarding the duty to warn for producers of unavoidably unsafe products.⁵²⁵ Such a duty is imposed only for foreseeable risks (but foreseeability is linked with the most up-to-date scientific knowledge available).⁵²⁶

⁵²² Owen D., *Products liability law*, pp. 677-678, presenting abundant quantitative research on the relevant case law. See also Goldberg R., *Medicinal Product Liability*, pp. 170-171; and in general Owen D., Montgomery J., Davis M.J., *Products Liability and Safety*.

⁵²³ Owen D., *Products liability law*, p. 675.

⁵²⁴ See the wording of the *Restatement (Second)* of Torts §402 A and the related discussion in Kysar D.A., “The Expectations of Consumers”, *Columbia Law Review* 103, 2003.

⁵²⁵ *Comment j* states: “The seller may reasonably assume that those with common allergies, as for example to eggs or strawberries, will be aware of them, and he is not required to warn against them. Where, however, the product contains an ingredient to which a substantial number of the population are allergic, and the ingredient is one whose danger is not generally known, or if known is one which the consumer would reasonably not expect to find in the product, the seller is required to give warnings against it, if he has knowledge, or by the application of reasonable, developed human skill and foresight should have knowledge, of the presence of the ingredient and the danger.”

⁵²⁶ See the leading cases *Brown v. Superior Court*, 751 P.2d 470 (California 1988) and *Beshada v. John Mansville Products Corp.*, 1001 N.J. 221 A.2d 1099 (New Jersey Supreme Court, 1982).

The ‘consumer expectation test’ has been the object of severe criticism, fundamentally based on the observation that, framed as it is in the *Restatement (Second)*, the test is somewhat amorphous and provides “eager and insufficient guidance to fact-finders charged with the difficult task of assessing the adequacy of a product design”.⁵²⁷ In response to these criticisms, the ALI produced the *Restatement (Third)* in 1998. As regards pharmaceutical products, it is noticeable that the new restated rules, to overcome potential harshness and vagueness, abandoned the straight interpretation of *comment j* and brought back the idea of “reasonableness”, moving away (*de facto* if not expressly) from strict liability, and introducing elements typical to negligence rules instead. Section 6(c) of the *Products Liability Restatement (Third)* provides: “A prescription drug or medical device is not reasonably safe due to defective design if the foreseeable risks of harm posed by the drug or medical device are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable health-care providers, knowing of such foreseeable risks and therapeutic benefits, would not prescribe the drug or medical device for any class of patients.”⁵²⁸ In other words, the new rule introduces a very narrow test for liability. While criticisms of the *Restatement (Second)* focused on its excessive scope, the *Restatement (Third)* has been rejected by certain commentators⁵²⁹ and the Nebraska Supreme Court⁵³⁰ for making recovery practically impossible. However, on balance, the new test has received the approval of leading scholarship as being “basically correct”⁵³¹ in comparison to the vague nature of the former rules.

3. The European Product Liability Directive for medicines

Turning to the EU attitude towards risk in liability claims, the European Product Liability Directive, while embracing a strict liability regime,⁵³² incorporates the idea of

⁵²⁷ Kysar D.A., “The Expectations of Consumers”, p. 1715.

⁵²⁸ *Restatement (Third) of Torts: Products Liability*, § 6(c).

⁵²⁹ See for example the contributions by Vandall F.J., “Constructing a Roof before the Foundation is Prepared: the Restatement (Third) of Torts: Products Liability, 2(b) Design Defect”, *University of Michigan Journal of Law Reform* 30, 1997; Conk G.W., “Is there a Design Defect in the Restatement (Third) of Torts: Products Liability?”, *Yale Law Journal* 109, 2000; Kysar D.A., “The Expectations of Consumers”.

⁵³⁰ In the case of *Freeman v. Hoffman La Roche Inc.* 260 Neb. 552, 618 N.W.2d 827, 2000.

⁵³¹ Goldberg R., *Medicinal Product Liability*, p. 41; Owen D.G., “Dangers in Prescription Drugs: Filling a Private Law Gap in the Healthcare debate”, *Connecticut Law Review* 42, 2010, p. 750.

⁵³² Council Directive 85/374/EEC on the approximation of the laws and administrative provisions of the Member States concerning liability for defective products, OJ 1985 L 210, arts. 1, 4, and 6.

‘development risk’, described by Jane Stapleton⁵³³ as a slightly more refined concept than its American counterpart. A ‘development risk’ is an unknowable risk that cannot be foreseeable because the state of scientific and technical knowledge, at the time the product is put into circulation, is not such as to enable the risk to be identified.⁵³⁴ The European Court of Justice has given a quite controversial interpretation of article 7(e) of the EU Directive 374/85 in the case *C-300/95 Commission v. United Kingdom*, stating that the provision is not specifically directed at the practices and safety standards in use in the industrial sector in question but concerns “unreservedly . . . the state of scientific and technical knowledge including the most advanced level of such knowledge”.⁵³⁵ The state of knowledge is, according to the Court, not that of which the actual producer “actually or subjectively was or could have been apprised, but the objective state of scientific and technical knowledge of which the producer is presumed to have been informed”.⁵³⁶ The Court does not develop this interpretation further. For instance, an explanation of the key phrase “state of knowledge”, and an accurate definition of “knowledge” as opposed to, for instance, a preliminary “hypothesis”, are absent.⁵³⁷ The very high standard that at first sight the Court sets for producers regarding discoverability is, moreover, limited by the next part of the Court's analysis. The only basis it offers for the presumption of the producer's knowledge of the defect is that the relevant knowledge must have been “accessible” at the time at which the product was put into circulation. However, no exact explanation of what the Court means by the word “accessible” is offered,⁵³⁸ thus leaving considerable margins of manoeuvre to national courts, and reintroducing an element of “reasonableness”⁵³⁹ that should be excluded by definition in strict liability.

⁵³³ In Stapleton J., *Products Liability*, London Butterworths, 1994.

⁵³⁴ Directive 374/85/EC, art. 7(e): “It shall be a defence for the producer to prove: . . . (e) that the state of scientific and technical knowledge at the time when he put the product into circulation was not such as to enable the existence of the defect to be discovered.”

⁵³⁵ Case C-300/95, *Commission of the European Communities v. United Kingdom of Great Britain and Northern Ireland* ECR 1997, I-02649, §26.

⁵³⁶ *Ibidem*, §27.

⁵³⁷ Mildred M., “The Development Risk Defence”, in Fairgrieve D., *Product Liability in Comparative Perspective*, Cambridge University Press, 2005, pp. 167-170. This discussion is developed in chapter VII.

⁵³⁸ Case C-300/95, *Commission v. United Kingdom*, §28.

⁵³⁹ The Court states explicitly that the relevant knowledge is meant to include “all data in the information circuit of the scientific community as a whole, bearing in mind, however, on the basis of a reasonableness test the actual opportunities for the information to circulate”: *ibidem*, §24. See chapter VII for a deeper discussion.

A necessary observation to make is that in parallel to the EU's Directive aimed at harmonising product liability legislation in the Member States, the field of pharmaceutical product liability presents a high degree of variability across the EU for two sets of reasons. On the one hand there are multiple and significant exceptions to the general regime, such as the provisions of the German Law regulating pharmaceuticals (*Arzneimittelgesetz*), and the Spanish Law (*Ley 22/1994, Sobre Responsabilidad Civil Por Danos Causados por Productos Defectuosos*), both providing a more 'pure' strict liability for pharmaceutical damages than that provided by the Directive as interpreted by the ECJ.⁵⁴⁰ This is not the place to discuss in depth the historical reasons that led to this situation. It is however worth recalling that it reflects a response to drug disasters in the course of the 20th century. Germany was heavily hit by the *Thalidomide* disaster. The legislation that was in place at that time (Germany was the first European country to have a special legislation for pharmaceuticals, adopted in 1961⁵⁴¹) appeared unable to sufficiently ensure drug security or provide a basis for recovery of damages by injured drug consumers. The new Act of 1976 purported to eliminate these deficiencies, establishing, among other provisions, strict liability claims in relation to damages caused by pharmaceutical products. In a recent case, the CJEU has confirmed the validity of the German provisions, even the amendments posterior to the entry into force of the Directive.⁵⁴² As regards Spain, the reasons are substantially similar, as the country has been hit by four major drug disasters in the space of three decades.⁵⁴³

On the other hand, in its interpretation of article 13⁵⁴⁴ of Directive 374/85/EC, the Court held that any scheme of product liability "founded on the same basis as that put in place by the Directive and not limited to a given sector of production does not come within any of the systems of liability referred to in article 13 of the Directive".⁵⁴⁵ On the basis of this reasoning, and considering pharmaceuticals as a specific "sector of

⁵⁴⁰ Reimann M., "Liability for defective products at the beginning of the twenty-first century: emergence of a worldwide standard?", and Wandt M., "German approaches to Product Liability", *Texas International Law Journal* 34, 1999.

⁵⁴¹ *Gesetz über den Verkehr mit Arzneimitteln*, 1961.

⁵⁴² Case 310/13, *Novo Nordisk Pharma GmbH v. S.*, ECR 2014.

⁵⁴³ See for a discussion Vega M.I.A., "The Defence of Development Risks in Spanish Law", *Consumer Law Journal* 144, 1997.

⁵⁴⁴ Article 13 provides: "This Directive shall not affect any rights which an injured person may have according to the rules of the law of contractual or non-contractual liability or a special liability system existing at the moment when this Directive is notified."

⁵⁴⁵ See Case C-183/00 *González Sánchez vs Medicina Asturiana SA* ECR 2002, I-3901.

production”, countries such as France and Italy have applied general tort law rules to pharmaceutical product liability claims.⁵⁴⁶ We will come back to these scenarios below.

4. A system’s reaction to major irritations: the US federal preemption of tort law

This section describes a recent trend in American pharmaceutical product liability litigation that exemplifies how the pharmaceutical regulatory system, as we identified it in the opening chapter, attempts to protect itself when subject to major irritations which challenge its self-sufficiency.

In 2006,⁵⁴⁷ a new doctrine (the doctrine of preemption) gained momentum in the sphere of drug litigation in the US. Until then, the FDA used to consider its risk/benefit analysis as setting a floor but not a ceiling for product safety. FDA approval would authorise a product to be marketed, but manufacturers would still be held responsible if a court later decided that a product was defective or a warning was inadequate. Over the past decade, however, this view had been called into question by regulators arguing that the FDA review process should set both floor and ceiling to foster marketing and availability of new products.⁵⁴⁸ Therefore, FDA approval of a new product should not simply indicate that the product can be marketed, but should be the final word in the safety assessment of that new product. The argument goes on, claiming that the threat of tort liability deters pharmaceutical companies and device makers from developing much-needed new technologies.⁵⁴⁹ Whenever those innovations are delayed if not abandoned altogether, “the

⁵⁴⁶ See among others Ponzanelli G., “Armonizzazione del diritto v. protezione del consumatore”, *Danno e Responsabilità*, 2002; and Busnelli F. D., Ponzanelli G., *La responsabilità del produttore tra legge speciale e codice civile*, in *Il danno da prodotti in Italia, Austria, Repubblica Federale di Germania, Svizzera*, a cura di S. Patti, Padova 1990.

⁵⁴⁷ Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (24 January 2006, effective June 30, 2006), 21 C.F.R. Pts. 201, 314, 601.

⁵⁴⁸ Sharkey C.M., “Federalism in Action: FDA Regulatory Preemption in Pharmaceutical Cases in State versus Federal Courts”, NYU School of Law, *Public Law & Legal Theory Research Paper Series*, n. 08-04, 2008; Sharkey C.M., “Preemption by Preamble: Federal Agencies and the Federalization of Tort Law”, *De Paul Law Review*, 56:227, 2007; Struve C.T., “The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation”, *Yale Journal of Health Policy, Law & Ethics*, 2005; IOM, “Regulatory Authorities for Drug Safety, in *The Future of Drug Safety – Promoting and Protecting the Health of the Public*, 2006.

⁵⁴⁹ Struve C.T., “The FDA and the Tort System”, p. 590; and see also for a discussion Philipson T.J., Sun E.C., Goldman D., “The effects of Product Liability Exemption in Presence of the FDA”, NBER

cost is felt not merely in financial terms but also in the suffering of people whose illnesses could have been treated with the new drug or device”.⁵⁵⁰ These critics argue that the tort system should not be permitted to re-determine product safety, as courts may unduly nullify the assessments of the FDA’s expertise.⁵⁵¹ the risk being that non-expert juries and judges will make weaker assessments in terms of scientific robustness and objectivity.⁵⁵² It has been strongly argued *contra*, however, that such a statement is inadequate because of the weakness of the FDA’s post-marketing surveillance process, essentially based on data furnished by the pharmaceutical industry itself, rather than autonomously managed by the agency.⁵⁵³ While the 2007 FDAA measures were supposed to balance this critical situation, as described in chapter V, the Avandia case suggests that post-marketing scrutiny is still underperforming.

The evolution of the relationship between product liability and product safety in the US shows a significant shift, in the past fifteen years, from a consumer-friendly to a much more producer-friendly tendency. It has been argued that the emergence of the doctrine of preemption promoted by the FDA can be explained in light of the agency’s need to regain authority and reliability after the Vioxx case described in chapter V. An argument could be made here that when confronted with a major irritation, the pharmaceutical *closed and self-perpetuating system* (as presented in chapter I) has tried to ‘defend itself’, moving the ‘capture’ of rule and decision-making power a step further: that is, by unilaterally shielding its decisions from any external influence and control.

Working Paper Series, 15603, 2009; Philipson T.J., Sun E.C., “Is the Food and Drug Administration Safe and Effective?”, NBER Working Paper Series, 13561, 2007.

⁵⁵⁰ Struve C.T., “The FDA and the Tort System”, p. 590.

⁵⁵¹ See the Preamble to Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934.

⁵⁵² Empirical data rather indicate that juries do better than their critics assert at handling technical issues, that juries are not as eager as some think to award damages against business defendants, and that punitive damages are awarded rarely in product liability suits (and mainly in cases involving egregious misbehaviour). See on the point Struve C.T., “The FDA and the Tort System”, pp. 592-593; more recently Hans V.P., “Judges, Juries and Scientific Evidence”, Cornell Law Faculty Publications, Paper 302, 2007; and chapter IX of this thesis.

⁵⁵³ There is abundant literature on the point. See the contribution by Carpenter D., *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA*, Princeton University Press, 2010. Older arguments asserting that the FDA’s reliance on the regulated company to supply the necessary safety data can lead to problems include McGarity T.O., “Beyond *Buckman*: Wrongful Manipulation of the Regulatory Process in the Law of Torts”, *Washburn Law Journal*, 41, 2002 (arguing that “[w]hen the onus is on the regulatee to provide data establishing that its product is ‘safe and effective’ . . . , the temptation is strong for a company to discount data indicating that the product may not meet the statutory test”); see also Noah B.A., “Adverse Drug Reactions: Harnessing Experiential Data to Promote Patient Welfare”, 49 *Catholic University Law Review*, 449, 470-471, 2000.

The doctrine of preemption initially attracted a surprising level of support from courts, for example from the New Jersey Supreme Court in the case *Rowe v. Hoffmann-La Roche Inc.* (March 2007). This endorsement was particularly surprising in light of the active and central role that the New Jersey Supreme Court had played in the historical development of product liability law, from the case *Beshada v. John Mansville Products Corp* to the famous *Feldman v. Lederle Laboratories*, applying section 402A of *Restatement (Second)* in its strictest interpretation.⁵⁵⁴ A turning point was however reached in March 2009, when the US Supreme Court, in *Wyeth v. Levine*,⁵⁵⁵ overruled the doctrine of preemption in drug litigation. In this decision, the opinion of the Court, delivered by Justice Stevens, clearly opines that state tort law cannot be considered an obstacle to the achievement of safety assessments by the FDA, but is rather a complement to it.⁵⁵⁶ The fact that no Congress statutes clearly provide a preemption clause for FDA's decisions goes in this very direction,⁵⁵⁷ and the majority opinions in *Wyeth* promote the idea of complementarity whereby regulatory compliance sets a minimum standard but not a definitive risk assessment.⁵⁵⁸

There is still room to question whether the preemption debate is over in drug litigation. On the one hand, as it appears from the facts of *Wyeth*, the defendant failed to disclose full information to the FDA regarding alternative and safer uses of the drug.⁵⁵⁹ More precisely, what the defendant was seeking in *Wyeth* was not a simple 'preemption defence', but a narrower 'impossibility by preemption defence'. In other words, the defendant was arguing that it could not introduce a new element (that is, the alternative safer use of the drug) in the labelling on its own motion, since the label had been approved by the FDA. As such, it argued, the state court was preempted from finding the

⁵⁵⁴ *Beshada v. John Mansville Products Corp*, 1001 N.J. Super. 221 A.2d 1099, 1982; *Feldman v. Lederle Lab.*, 257 N.J. Super. 163, 1992.

⁵⁵⁵ *Wyeth v. Levine*, 129 S.Ct. 1187, 2009.

⁵⁵⁶ *Ibidem*, opinion of the Court, Part IV.

⁵⁵⁷ In pharmaceutical product cases, implied preemption was applied by considering federal agency (FDA) determinations as substitutes for Congressional intent. Deferring to the agency position on preemption of state common law is however troublesome: see for a general discussion Davis M.J., "The New Presumption against Preemption", *Hastings Law Journal*, 61, 1217, 2010.

⁵⁵⁸ As implied by scholars such as Owen D.G., "Dangers in Prescription Drugs: Filling a Private Law Gap in the Health Care debate", *Connecticut Law Review*, 42, 2010, p. 733 ff, noting "the continued decline of the federal preemption doctrine as a bar to warning adequacy claims against drug manufacturers"; but see also Ausness R.C., "The Impact of *Wyeth v. Levine* on FDA Regulation of Prescription Drugs", 65 *Food & Drug Law Journal* 247, 2010, suggesting a more cautious approach.

⁵⁵⁹ *Wyeth v. Levine*, 129 S. Ct. 1187, opinion of the Court, Part III.

claimant liable for failure to warn.⁵⁶⁰ On the other hand, and on a more general note, the Court rejected Wyeth's argument that tort claims "interfere with Congress's purpose to entrust an expert agency to make drug labeling decisions that strike a balance between competing objectives",⁵⁶¹ holding that such an argument relies on an "untenable interpretation" of congressional intent and an "overboard view" of an agency's power to preempt state law.⁵⁶² This statement has the effect of narrowing down substantially the space for implied preemption, and claiming back for state institutions the power to decide when and how individuals should be put in the conditions to react against procedures and decisions that affect them.

Notwithstanding the clear wording of this particular judgment, it might be too early to argue that federal preemption cannot be invoked *tout court* in drug cases (whereas it seems hardly disputable that it is precluded when the defendant fails to operate proactively on the basis of all information in his possession). As colourfully noted by Mary Davis, "trying to make sense of preemption opinions [of the Supreme Court] reminds one of being on a roller coaster [...]. The uncertainty of where the coaster will go, while exhilarating for the time, is also exhausting and frustrating".⁵⁶³ A fair comment, if we compare *Wyeth* with the previous high-profile implied preemption case decided by the Supreme Court, *Riegel v. Medtronic, Inc.*,⁵⁶⁴ where the Court displayed a significantly broader approach to the issue.⁵⁶⁵ Further, another quite significant and distinct decision was taken two years after *Wyeth* in the case of *PLIVA, Inc. v. Mensing*.⁵⁶⁶ The Court in the *PLIVA* case established a *de facto* 'two-tier drug liability system' by recognising that in the realm of generic drugs, the doctrine of preemption can still be relied upon.⁵⁶⁷

⁵⁶⁰ *Ibidem*, opinion of the Court, Part III: the Court concluded on this point that "[i]mpossibility preemption is a demanding defense. [...] Wyeth has failed to demonstrate that it was impossible for it to comply with both federal and state requirements. The CBE regulation permitted Wyeth to unilaterally strengthen its warning, and the mere fact that the FDA approved Phenergan's label does not establish that it would have prohibited such a change."

⁵⁶¹ *Ibidem*, opinion of the Court, Part IV.

⁵⁶² *Ibidem*.

⁵⁶³ Davis M.J., "On Restating Products Liability Preemption", *Brooklyn Law Review*, 74, 2009, p. 776, noting the level of inconsistency in Supreme Court judgments on preemption over the last two decades.

⁵⁶⁴ *Riegel v. Medtronic, Inc.*, 128 S. Ct. 999, 2008, pp. 1007-1008.

⁵⁶⁵ Davis M.J., "On Restating Products Liability Preemption", pp. 770 – 771.

⁵⁶⁶ *PLIVA, Inc. v. Mensing* 131 S. Ct. 2567, 2011.

⁵⁶⁷ The case and the two-tier litigation are well discussed in Goldberg R., *Medicinal Product Liability*, p. 150 ff.

5. The necessary relationship between regulation and product liability

The questions for the purposes of this work are whether the tort law rules briefly recalled above are, by their nature, able to complement regulation through the delivery of a higher standard of scientific knowledge; whether these rules are able to exercise effective control over the outcome of regulation; and how they interact with said regulation.⁵⁶⁸

The regulatory and litigation systems could theoretically operate entirely independently, as they are two separate and independent bodies of law. It seems however unrealistic to advocate total independence: “it seems clear that the agencies’ expert assessments of product safety should not be irrelevant in litigation arising from asserted safety defects. Rather, the dispute is over what the *effect* of the agency’s safety determinations should be.”⁵⁶⁹ Given that even in the absence of formal connections an interplay between the two regimes exists, the question becomes how to make it work to promote best availability of knowledge that is relevant for safety assessments, and to exercise a control that we have defined as legitimating for the relevant regulatory process.

As noted above, for a period of time in the US the FDA’s expert balancing of product risks and benefits was interpreted as leaving no room for disagreement within the tort system (indeed, this is still the case for generic products) on the basis that there could be no justification for tort claims to ‘second-guess’ the FDA’s judgements, and such second-guessing would be likely to produce undesirable results when rejecting experts’ assessments.⁵⁷⁰ However, it has also been pointed out that the FDA cannot foresee and address all product safety issues ahead of time, and that the agency may not have the ability to respond quickly enough to issues when they first arise after a product enters the market.⁵⁷¹ Courts, in the process of considering the effects of agency determinations, have

⁵⁶⁸ The specificities of each category of toxic products is such that a certain degree of separation from other fields is inevitable. However, for a comprehensive account of the legal and moral aspects of the debate around regulation and litigation in the field of tobacco, see the essential Howells G., *The Tobacco Challenge*, Ashgate, 2011.

⁵⁶⁹ Struve C.T., “The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation”, p. 609.

⁵⁷⁰ See Davis M.J., “The Battle over Implied Preemption: Products Liability and the FDA”, *Boston College Law Review*, 48, 2008, pp. 1089-1094; Davis M.J., “Discovering the boundaries: Federal Preemption of Prescription Drug Labeling Products Liability Actions”, *University of Kentucky Law Journal*, 2005. This was to some extent already suggested by Posner R., *Economic Analysis of Law*. 5th ed., New York, Aspen Publishers, Inc., 1998.

⁵⁷¹ In addition to the discussion laid down in chapter V, several authors have stressed the shortcomings of FDA regulation: see among others Davis M.J., “The Battle over Implied Preemption: Products Liability and the FDA”, Davis M.J., “Discovering the boundaries: Federal Preemption of

constantly balanced these competing considerations. The 2006 departure from the traditional approach, with the FDA autonomously establishing that certain types of its determinations should preclude litigation altogether, presented major issues. As correctly identified by the US Supreme Court in *Wyeth*, a total detachment of the regulatory system from any form of external influence and oversight is undesirable. The impact of the *PLIVA* decision in preempting tort claims related to generics will have to be measured in time.

It has been accurately argued that permitting FDA approval to preclude the possibility of tort liability does more than ensure that product safety decisions are reserved to the FDA, because preemption of tort litigation removes the opportunity for litigation to proactively complement the FDA's activity of monitoring product safety.⁵⁷² Moreover, taking into account the classic compensatory function of tort law, preemption *de facto* denies compensation to persons harmed by a product by the mere fact of that product having been approved by the agency, even if they were harmed after a safety problem first emerged but before the FDA took regulatory action to remove the product from the market or require additional warnings⁵⁷³ (Vioxx and Avandia provide two easy examples).

The pharmaceutical regulatory system is complex and vulnerable as described in the previous chapters. Christopher Hodges asserts that "it is undoubtedly true that the system is complex and provides a number of competing interests which a properly regulated society must seek to balance".⁵⁷⁴ To describe the scenario, the term "multi-regulation"⁵⁷⁵ has been used by scholars. The very considerable sums of money

Prescription Drug Labeling Products Liability Actions", and Struve C.T., "The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation"; and *contra* see Philipson T.J., Sun E.C., Goldman D., "The effects of Product Liability Exemption in Presence of the FDA", and Philipson T.J., Sun E.C., "Is the Food and Drug Administration Safe and Effective?".
⁵⁷² Struve C.T., "The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation", p. 615 ff.; a conclusion upheld by the US Supreme Court in *Wyeth*.

⁵⁷³ This is the case more often than one might think due to the weaknesses of the FDA's post-marketing surveillance system. The issue is raised by, among others, IOM, "Regulatory Authorities for Drug Safety", in *The Future of Drug Safety – Promoting and Protecting the Health of the Public*; Philipson T.J., Sun E.C., Goldman D., "The effects of Product Liability Exemption in Presence of the FDA"; Philipson T.J., Sun E.C., "Is the Food and Drug Administration Safe and Effective?"; and Struve C.T., "The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation", who accurately describes the differences in the budgets dedicated to the post- as opposed to the pre- marketing surveillance procedures, the post-marketing being underfunded and less than perfectly organised.

⁵⁷⁴ Hodges C., *European Regulation of Consumer Product Safety*, p. 47.

⁵⁷⁵ *Ibidem*, quoting Hancer L., "Pharmaceutical Policy and Regulation: Setting the Pace in the European Community", in Davis P., *Contested Ground: Public Purpose and Private Interest in the Regulation*

involved in the success or failure of pharmaceutical products⁵⁷⁶ can be distracting. It is correspondingly important in this sector that there should be “continuous confidence in the appropriateness and strength of the design and operation of the system, and rigorous compliance with its regulatory standards, through periodic review of its operation and transparency”.⁵⁷⁷ While in chapter V the Vioxx and Avandia cases were presented as neutrally as possible, they invite consideration of possible claims of misconduct, suggesting potential systemic bias, secrecy, and the potential for fraudulent production of safety data, especially in toxicology or clinical research.⁵⁷⁸ The Vioxx case alone, in which Merck failed to disclose relevant safety data relating to known potential risks of cardiovascular ADRs, demonstrates that such concerns are not groundless.⁵⁷⁹ In this sense, the decision of the Supreme Court in *Wyeth* is to be welcomed and supported as a positive reaction to a misplaced attempt to isolate an imperfect regulatory system from necessary balancing mechanisms.

6. The European form of pharmaceutical product liability preemption

The European scenario suggests different reflections. Regulatory compliance is not considered proof of safety. The only defence explicitly mentioning

of Prescription Drugs, Oxford University Press, 1996.

⁵⁷⁶ Boston Consulting Group, *A Revolution in R&D: How Genomics and Genetics are Transforming the Biopharmaceutical Industry*, Boston, 2003; DiMasi J., Hanson R.W., Grabowski G., “The Price of Innovation: New Estimates of Drug Development Costs”, *Journal of Health Economy*, 22, 2003, pp. 51-185; Rawlins M.D., “Cutting the Costs of Drug Development?”, *Nature*, 3, April 2004, p. 360; see a more recent account by Herper M., “How Much does Pharmaceutical Innovation Cost? A Look at 100 Companies”, *Forbes*, 2013.

⁵⁷⁷ See the discussion in chapters I and II; Hodges C., *European Regulation of Consumer Product Safety*, p. 48; and Medawar C., Hardon A., *Medicines Out of Control? Antidepressants and the Conspiracy of Goodwill*, Amsterdam 2004, and its review Collier J., “Regulating Regulators”, *the Lancet*, 363, June 2004. In this light, for the American scenario, see Avorn J., MD, *Powerful Medicines - The Benefits Risks and Costs of Prescription Drugs*, Vintage Books, 2005. For a converse view that medicine safety is well regulated, see Silcock J., Pritchard C., *To Heal and to Harm: An Economic View of Drug Safety*, London, Routledge, 2003; Kanavos P., Ross-Degnan D., “Measuring, Monitoring and Evaluating Policy Outcomes in the Pharmaceutical Sector”, in Mossialos E. et al., *Regulating Pharmaceuticals in Europe: Striving for Efficiency, Equity and Quality*, Open University Press, 2004.

⁵⁷⁸ For discussion of whether unfavourable studies may not be published or reported quickly enough, see Hylton K., “Preemption and Product Liability, a Positive Theory”, *Boston University School of Law*, WPS n.03-17, 2005; from a more ‘journalistic’ perspective, see “SSRIs: Suicide Risk and Withdrawal”, 361 *the Lancet*, June 2003; Laurance J., “*Sexorat* Ban Raises Doubts over Drug Licensing System”, *The Independent*, 11 June 2003. Progress is expected in the EU thanks to the new regulatory framework.

⁵⁷⁹ See chapter V and in particular the discussion of delays in risk communication.

regulatory requirements is the one provided by article 7(d) of the Product Liability Directive⁵⁸⁰ – on the basis of which a producer will be shielded from liability where “the defect is due to compliance of the product with mandatory regulations issued by public authorities”. Short of that, compliance with regulatory requirements is not an automatic defence for manufacturers.

The problems lie elsewhere. The EU has traditionally maintained a different approach to redress in case of damages (and generally to correction of regulatory failures), relying heavily on compensation and indemnification schemes based on insurance and social security systems rather than on tort litigation.⁵⁸¹ Arguably, this has created a sort of *de facto* preemption of product liability litigation. The aggregate statistics on product liability litigation in the EEA over a time span of twenty years, collected by the Commission in a series of quinquennial reports from 1995 to 2011,⁵⁸² confirm that European product liability has faced structural obstacles in attaining a primary role in victims’ compensation. It is beyond the scope of this chapter to analyse in depth the range of reasons leading to this observation, but it is possible to identify some essential factors. In 2003 Mathias Reimann identified five explanations⁵⁸³ for why product liability litigation is a major feature of the American legal system while it lags behind in Europe (and in the rest of the world in his analysis). These explanations have to do with institutions (US courts being traditionally more activist than the European ones – relying on specific features ranging from the role of juries to exponentially higher damage awards),⁵⁸⁴ procedures (the much higher availability of aggregate litigation in the US makes it dramatically easier for plaintiffs to prove the existence of both defect and causation, not to

⁵⁸⁰ Council Directive 85/374/EEC on the approximation of the laws and administrative provisions of the Member States concerning liability for defective products, OJ 1985 L 210.

⁵⁸¹ As thoroughly explained, in an analysis that remains substantially valid over ten years later, in Reimann M., “Liability for defective products at the beginning of the twenty-first century: emergence of a worldwide standard?”, 51 *American Journal of Comparative Law*, 2003) 751. See brief discussion in the text.

⁵⁸² Commission Report, *First report on the application of Directive 85/374/EEC concerning liability for defective products* COM(1995) 617 final; Commission Report, *Second report on the application of Directive 85/374/EEC concerning liability for defective products* COM(2000) 893 final; Commission Report, *Third report on the application of Directive 85/374/EEC concerning liability for defective products* COM(2006) 496 final; Commission Report, *Fourth report on the application of Directive 85/374/EEC concerning liability for defective products* COM(2011) 547 final. The reports show the low impact of product liability litigation in the EEA, with a tendency to increase over the years as discussed *infra*.

⁵⁸³ Reimann M., “Liability for defective products at the beginning of the twenty-first century”.

⁵⁸⁴ *Ibidem*, pp. 807 and 812-816.

mention the availability of stronger discovery rules),⁵⁸⁵ the legal profession (European lawyers have a much lesser tendency to specialise than their US colleagues),⁵⁸⁶ the role of insurance (first party insurance is still the European prime method of victims' compensation, through public or semi-public or private insurance, and/or no-fault compensation schemes),⁵⁸⁷ and the broader social environment (the level of publicity that product liability law receives in the EU, from media attention to the political debate, is simply incomparable to the US scenario).⁵⁸⁸ A common assumption underlying this divergence between the two sides of the Atlantic is that the EU is politically committed to achieving product safety through public (or publicly administered) regulatory requirements whereas the US relies more substantially on private litigation.⁵⁸⁹

However, a closer look at the recalled Commission Reports on the application of the Product Liability Directive in the EEA shows a progressive increase in the volume of litigation and out of court settlements.⁵⁹⁰ The reasons identified are an increase in "consumer awareness, better organisation of consumer groups or improved means of accessing information".⁵⁹¹ While these explanations certainly play a significant role, we submit that there is more to the picture. Recent cases have called into question the reliability of the well-established European regulatory architecture for pharmaceuticals.⁵⁹² Aggressive litigation in France on the widely dispersed medicine *Mediator*⁵⁹³ has led to a withdrawal of the product from the market, signifying the existence of renewed scope for a complementary approach.

This observation is corroborated at a more general level by Daniel Kelemen who has recently argued that the European Union is progressively shifting towards a model of

⁵⁸⁵ *Ibidem*, pp. 816-822.

⁵⁸⁶ *Ibidem*.

⁵⁸⁷ *Ibidem*, pp. 822-832. See also the series of Commission Reports referred to *supra*.

⁵⁸⁸ Reimann M., "Liability for defective products at the beginning of the twenty-first century", pp. 832-835.

⁵⁸⁹ *Ibidem*, p. 810; see also Hodges C., European Regulation of Consumer Product Safety; Howells G., "The Relationship Between Product Liability and Product Safety – Understanding a Necessary Element in European Product Liability Through a Comparison with the US Position", 39 *Washburn Law Journal*, 2000.

⁵⁹⁰ Commission Reports 1995-2011, referred to *supra*; see also Lovells, *Product Liability in the European Union, A report for the European Commission* (2003) MARKT/2001/11/D, p. 39, discussing the progressive increase in out of court settlements.

⁵⁹¹ Commission Report, *Fourth report on the application of Directive 85/374/EEC concerning liability for defective products* COM(2011) 547 final, p. 4.

⁵⁹² See the brief description *supra* in section 2 of this chapter.

⁵⁹³ See the latest judgment in a prolonged saga – Tribunal Administratif de Paris, n. 1312345/6 (2014). Civil litigation involving the producer *Laboratoire Servier* is still pending.

‘adversarial legalism’ (or Eurolegalism). This developing model departs from the traditional heavy and quasi-exclusive reliance on regulators and technical bureaucracies in favour of judicial litigious mechanisms – a European version of regulation through litigation.⁵⁹⁴ This convergence of US and EU towards a judicialisation of regulatory matters requires a discussion of both the EU liability rules (and subsequently of their accessibility which will form the object of chapter VIII).

7. Uncovering the EU pharmaceutical product liability fragmentation

Aside from the difficulties in establishing a consolidated litigation practice, the EU scenario poses two fundamental questions concerning (1) the harmonisation of liability rules, and (2) the links between the systems of regulation and liability. The two problems are to some extent related.

(1) As regards tort law, harmonisation of pharmaceutical product liability in Europe remains unachieved, for two substantial reasons. The first and most obvious one is the presence of special regimes specifically put in place in this field by some Member States, especially Germany and Spain as recalled above. The second reason is that the implementing process of the EC Directive 374/1985 on Product Liability has been long and complex, and the outcomes are still not entirely clear, due to the reluctance of the Member States to retreat from their judicial and doctrinal interpretations of the subject in favour of a centralised model that is, at least in some cases (like France or Italy), less favourable for the consumer. With its rulings of year 2002⁵⁹⁵ (a position maintained in 2014) the Court of Justice has clarified that the model provided by the Directive, despite the literal wording of article 13,⁵⁹⁶ has to be considered the only general system of product liability in the EU, and that parallel regimes can survive only if they provide liability systems of a different type, or special liability systems relating to specific types of

⁵⁹⁴ Kelemen R.D., *Eurolegalism*, Harvard University Press, 2011; and Kelemen R.D., “Eurolegalism and Democracy”, *Journal of Common Market Studies* 50, 2012; see also the analysis by Strong S.I., “Regulatory Litigation in the European Union: Does the U.S. Class Action Have a New Analogue?”, *Notre Dame Law Review* 88, 2012.

⁵⁹⁵ Case C-52/00 *Commission v. France* [2002] ECR I-3827 and Case C-183/00 *González Sánchez v. Medicina Asturiana SA* [2002] ECR I-3901.

⁵⁹⁶ Directive 374/85/EC, article 13: “The Directive shall not affect any rights which an injured person may have according to the rules of contractual or non-contractual liability or a special liability system existing at the moment when this Directive is notified.”

products. That means, as a consequence, that the ruling of the ECJ in the case of *Commission v. United Kingdom*,⁵⁹⁷ on the proper meaning of the development risk defence, has to be considered the definitive interpretation of the defence across Europe in the application of the Directive. So in the Member States in which pharmaceutical cases are subject to the Directive's regime, a producer will be held to the Directive's standard, whereas in Member States having a special regime, the producer will be held to a different standard. There is more. In Member States applying general tort law provisions to specific products (such as pharmaceuticals), the standard the producer will have to reach will change again. In Germany, plaintiffs are able to obtain full compensation under the *Arzneimittelgesetz* by proving that they suffered damages from the contested pharmaceutical product.⁵⁹⁸ The producer is responsible on a strict liability basis with supplementary duties to provide information.⁵⁹⁹ Elsewhere, in England, a producer will be able to defend himself if he proves that the damage came from a development risk, as interpreted by the Court of Justice, meaning that knowledge of the risk (if it existed at the moment the product entered the market) was not reasonably and objectively accessible and obtainable for the producer.⁶⁰⁰ Finally, in Italy, if we assume the applicability of article 2050 cc⁶⁰¹ to this type of claim,⁶⁰² for the producer to avoid liability the burden of proof is harsher than under the Directive's regime, since the defendant has to show he took "all appropriate measures to avoid the damage", in the way such a provision is interpreted by the courts.⁶⁰³

⁵⁹⁷ Case C-300/95 *Commission of the European Communities v. United Kingdom of Great Britain and Northern Ireland* ECR 1997, I-02649.

⁵⁹⁸ *Arzneimittelgesetz* § 84. How 'simple' that is in practice is an entirely different issue, which goes to the core of the dynamics of the tort system, involving its accessibility. The issue will be explored below through case studies.

⁵⁹⁹ This will be discussed in greater detail in chapters VII and VIII.

⁶⁰⁰ This interpretation suggests a substantial analogy with the negligence regime that is provided by s. 6(c) of the Restatement (Third) on Torts.

⁶⁰¹ Article 2050 of the Italian civil code provides: "Chiunque cagiona danno ad altri nello svolgimento di un'attività pericolosa, per sua natura o per la natura dei mezzi adoperati, è tenuto al risarcimento, se non prova di avere adottato tutte le misure idonee a evitare il danno".

⁶⁰² Which can be the case if we consider that general tort law rules can be applied as special liability rules for specific types of products (as pharmaceuticals are). See case Cass civ., 29 April 2005, n. 8981: "Posto che la disciplina della responsabilità da prodotti difettosi *si affianca e non si sostituisce alla disciplina codicistica sulla responsabilità per danno* [...] il produttore risponde dei danni cagionati dal vizio di progettazione del suo prodotto qualora siano provati la sua colpa nella causazione dell'evento, ed il nesso causale tra il vizio della cosa ed il pregiudizio."

⁶⁰³ The producer has to show positively that he took all possible measures and techniques to avoid the damage, even the most advanced and abstractly possible ones, no matter the costs or the feasibility; for a discussion see Recano P., *La responsabilità civile da attività pericolose*, CEDAM, 2001, pp. 200-210.

(2) The second question goes with the first. How are the regulatory and litigation systems linked? There are two interesting provisions in the EC Directive 2001/83 on pharmaceutical safety. The first is in article 25: “Authorisation *shall not affect the civil and criminal liability* of the manufacturer and, where applicable, of the marketing authorisation holder.” The second is in article 61.4: “The fact that the competent authority does not refuse a marketing authorisation pursuant to paragraph 2 or a change to the labelling or the package leaflet pursuant to paragraph 3 *does not alter the general legal liability* of the manufacturer or as appropriate the marketing authorisation holder.”

What is “the general legal liability of the manufacturer”? To which regime of civil liability does Directive 2001/83 refer itself? Aims of systemic coherence would suggest that it refers to the Product Liability Directive, which was intended to cover “all movables”, therefore including pharmaceuticals – with the exception of countries such as Germany with specific exceptional liability regimes. That is the case for example in the UK. But here arises a problem of linkage between the two regimes. The Product Liability Directive, given the defence provided by article 7(e), limits its effects to the moment the product enters the market. The relevant knowledge to be considered to assess a producer’s liability is the knowledge available at that moment. The ECJ made this point clear in its ruling against France⁶⁰⁴ (the implementing legislation of which rendered the development risk defence available only to the producer that could prove ten years’ monitoring after the product entered the market).⁶⁰⁵ The problem is the quality of that knowledge, which arises from a procedure that appears to be structurally fragmented, with uncertain results. It has been pointed out that such an outcome is paradoxical.⁶⁰⁶ Liability rules, which are supposed to play a role *ex post* in risk management, are bound to the *ex ante* state of knowledge, whereas regulation (with the pharmacovigilance system) is taking care of the *ex post* (through the pharmacovigilance and the post-marketing surveillance powers of regulatory agencies), notwithstanding that regulation is typically meant to prevent adverse events (and therefore to play its role mainly *ex ante*).⁶⁰⁷ In other words, for pharmaceutical products, the Product Liability Directive does not seem to work. And in the light of enhancing consumer safety, such fragmentation works to the detriment of both access to

⁶⁰⁴ Case C-52/00 *Commission v. France*.

⁶⁰⁵ This legislation was overruled explicitly because the two fields were meant to be kept separated.

⁶⁰⁶ Cafaggi F., *The institutional framework of European Private Law*, p. 191 ff.

⁶⁰⁷ *Ibidem*.

justice and the level of protection in practice (if damages occur outside the boundaries of the Directive and the consumer has to sue in negligence, he will have to prove the fault of the defendant, which is, as has been exhaustively discussed by lawyers and scholars, extremely difficult).⁶⁰⁸ Basically, in countries where pharmaceuticals undergo the discipline of the Product Liability Directive, the link between regulation and liability provides a shape-shifting liability regime, depending on the timing of the damage and of the related imperfect knowledge.

Interesting scenarios are those of countries that apply general tort law provisions as special product liability regimes for pharmaceutical products. In Italy, the application of article 2050 cc as interpreted by the courts fits quite well with the idea of complementing the regulatory system's decisions, as it ensures the possibility of cross-fertilisation between the two systems, the latter being likely to be enriched by the outcomes of litigation.⁶⁰⁹ First, in any case of damage caused by pharmaceuticals, the Italian judicial model of pharmaceutical product liability ensures the applicability of the same regime regardless of the timing of the damage and of the related knowledge (contrary to those countries where pharmaceuticals are subject to the Directive's regime). Secondly, there is no development risk defence (which implies a 'negative proof' that the state of knowledge was not such as to enable the existence of the defect to be discovered, with all the uncertainties related to 'state of knowledge' brought in by such a defence), but rather a positive burden of proof upon the producer to prove that he took 'all appropriate measures', as noted above.⁶¹⁰

⁶⁰⁸ A few words to recall the origins of product liability in the US and the EU: in both scenarios, the first concern was to shift the burden of proof from the claimant to the defendant, in order to balance the asymmetric distribution of information and economic means. For an overview see among others Ponzanelli G., *La responsabilità civile - Profili di diritto comparato*, Il Mulino, 1992.

⁶⁰⁹ See among others Green M.D., "Statutory Compliance and Tort Liability: Examining the Strongest Case", *University of Michigan Journal of Law Reform* 30, p. 482 ("Sometimes it is the tort system that uncovers instances of non-compliance with FDA regulatory standards, rather than the FDA itself."); and in general Viscusi K. (ed.), *Regulation through Litigation*, AEI Brookings Joint Center for Regulatory Studies, 2002, and Kelemen R.D., *Eurolegalism*.

⁶¹⁰ See the discussion *supra*, and the Italian cases Cass civ., 29 April 2005, n. 8981; Tribunal of Venice, 14 February 2005; Tribunal of Rome, 20 April 2002, *Diritto e Giustizia*, 2002; Cass civ. 27 July 1991 n. 8395, *Rep. Foro It.*, 1992; Cass civ. 15 July 1987 n. 6241, *Foro It.*, 1988.

8. A renewed role for old rules?

What can we make of this analysis for the purposes of this study? This question will be developed in the following three chapters through a discussion of significant case law, and finally turned into a normative claim in the final chapter. It is however necessary to embed the analysis of product liability rules in the larger discourse of this thesis.

Unsurprisingly, product liability rules tend to be very narrow in the identification of the legal matter to be litigated and solved. The overview suggests that the two classic roles are in play, compensation and deterrence, with a higher emphasis on one or the other, depending on the national system at stake. The attempt here is to move forward and push the boundaries of the liability laws towards a new role, which we have defined as a ‘pedagogical’ one. Such a move requires courts to overcome their natural deference to formal regulatory compliance, questioning not only the presence of a defect in a litigated product, but, more to the point, the *origins* of such a defect, beyond the boundaries of mere negligence or strict liability.

There is in other words room to call for a move in courts’ attitude to surpass the walls of party-party litigation, entering the broader (but essential) space of regulatory compliance in its substantial dimension: does the permeation of exogenous elements into domestic frameworks described in chapter III compromise the quality of the regulatory assessment and its compliance with said domestic requirements? And does the safety delivery provided by the regulatory system as described in chapter V provide a legitimate basis for deference? The questions may seem far-fetched, but the overview of liability rules we have just provided seems to open the door to a margin of manoeuvre for judges to side-step the impasse and reframe the issue: why, given the requirements laid down by law, does a product formally compliant with said requirements harm consumers? Mere scientific uncertainty, fault, or flaws in a regulatory framework allowing second-best assessments? This would be the idea of a ‘hard look doctrine’ applied to the pharmaceutical regulation of safety, an idea that we will develop in the final chapter after questioning to what extent it is feasible and realistic to rely on courts for improving data quality, legitimacy, and safety delivery.

CHAPTER VII

RELYING ON COURTS 1

IMPROVING SCIENTIFIC DATA QUALITY AND AVAILABILITY?

What now requires analysis is the judiciary's contribution to the availability and quality of scientific data, the levels of participation understood in terms of access to justice, and the delivery of safety.

This chapter tackles the first aspect. Evidence suggests that through judicial intervention, scientific evidence that gets lost or withheld in the regulatory process can be uncovered and integrated in specific risk assessments, or made generally available for more diverse purposes. As the first section will discuss, through focused interventions courts can impact access to information beyond the boundaries of a single case – and arguably all the way to legislative reform. While the oversight thus provided is occasional and necessitates a more diffuse and continuous supplement, the outcome, as shall be discussed, is potentially far reaching. The second section engages with the fundamental issue of partial data. There appears to be a significant level of awareness within the judiciary regarding the flaws of the regulatory framework counterbalanced by a generally deferential approach to regulatory findings which typically restrains courts from questioning the origin of emerging safety issues – the regulatory architecture itself – confining the enquiry exclusively to specific conduct instead.

1. Breaking the circle: data availability through court intervention

The first step in discussing courts' ability to improve accessibility of data, and consequently the quality of regulatory assessments, requires an analysis of court cases directly impacting the disclosure of new scientific evidence. In this sense, the analysis can move forward from the observation suggested in chapter V during the discussion of the

Avandia case. As recalled, the turning point of the prolonged saga of *Rosiglitazone* occurred in 2007 with a research initiative conducted by a group of scientists who published in the *NEJM* a meta-analysis on cardiovascular ADRs related to the successful anti-diabetes medicine.⁶¹¹ What is interesting for the purposes of this chapter is the enabling factor that allowed the *NEJM* scientists to access essential unpublished trials data. Upon the initial refusal of GSK to release relevant data (a surprising move, one might think, in light of what follows), scientists discovered that a 2004 settlement had imposed full disclosure on the company as of December 2000.⁶¹² The settlement was a result of the case *People of the State of New York v. GlaxoSmithKline*, initiated by the State Attorney General, Eliot Spitzer, in the Supreme Court of New York.⁶¹³ The case involved an antidepressant of the widely popular SSRI (selective serotonin reuptake inhibitor) class, *Paroxetine* (commercially branded as Paxil by GSK)⁶¹⁴. The AG's case was built on a series of previous lawsuits⁶¹⁵ launched across the US seeking compensation for severe ADRs related to the use of Paxil – including an alleged significant increase in suicidal and homicidal tendencies, especially in child and adolescent populations.⁶¹⁶ A particularly contentious element of the case was, in Spitzer's submission,⁶¹⁷ the fact that prescription to juvenile populations was an 'off-label' use – that is, a use different than what is prescribed by the authorised label, typically under the direction of a physician. While legal *per se*,⁶¹⁸ the problematic aspect in the case at hand

⁶¹¹ The meta-analysis showed an increase in the risk of cardiovascular ADRs of up to 40% associated with the use of Avandia: Nissen S.E., Wolski K., "Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes", *New England Journal of Medicine* 356, 2007.

⁶¹² See the account of the principal investigator of the *NEJM* study, Nissen S.E., "The Rise and Fall of Rosiglitazone", *European Heart Journal* 31, 2010, p. 774: "The manufacturer of rosiglitazone declined [access to trials data]. Then serendipity intervened. In 2004 the state of New York had sued GSK alleging that the company had failed to publish the results of unfavourable studies [...]".

⁶¹³ *People of the State of New York v. GlaxoSmithKline*, filed on June 2, 2004 – case file available at <http://news.findlaw.com/wp/docs/glaxo/nyagglaxo60204cmp.pdf>.

⁶¹⁴ See FDA Approval Letter for NDA 20-031/026, retrievable from Paxil 'Drug Approval Package', available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/20-031S026_Paxil.cfm.

⁶¹⁵ For example, a class action was filed in August 2001 in Los Angeles focused on the withdrawal symptoms; in September 2001 a case was filed in Philadelphia and another in Wyoming alleging violent outbursts related to Paxil use – see the discussion *infra*.

⁶¹⁶ In particular, the Wyoming case highlighted that the risk of increased violence and/or suicidal tendencies related to Paxil was known and inadequately warned for as a theoretical possibility (especially in juvenile populations) at the time of marketing approval: see *Estates of Tobin Ex Rel. Tobin v. SmithKline*, 164 F.Supp. 2d 1278 (D. Wyo. 2001).

⁶¹⁷ *People of the State of New York v. GSK*, case file, p. 2.

⁶¹⁸ An off-label prescription entails the use of the medicine for a non-approved therapeutic indication, age range population, dosage or method of administration. Physicians are legally allowed to prescribe off-label within strict ethical guidelines, all of which require full disclosure of relevant information. See the US FDAMA (discussed in chapter II). In Europe off-label prescription regulation is left to Member States, which in general endorse the possibility of relying on physicians' expertise (Italian and French regulatory authorities are particularly active in the

was the strong commercial campaign that had been launched by GSK to promote said off-label use of Paxil to both the public and physicians.⁶¹⁹

A short parenthesis is required at this point. One of the elements which recurrently emerged in the analysis offered in chapter V was the presence and availability on the market of treatments similar or alternative to the problematic new products (this was observed both for Vioxx and for Avandia).⁶²⁰ In a class-specific version of the same problem, in the case of SSRI antidepressants, the first medicine of the class to hit the market was *Fluoxetine* (marketed by Eli Lilly as Prozac).⁶²¹ Following the swift success of this new type of depression treatment, a series of ‘me too drugs’ hit the market in rapid succession (such as Pfizer’s Zoloft and Paxil itself). A me too drug is a medicine structurally very similar to a product already on the market, with only minor variations in the chemical composition, typically targeting the same patient population.⁶²² Of the various SSRIs marketed at the time, only Zoloft was initially approved for prescription to minors.⁶²³ However, the need to aggressively market a product minimally diverging from the ‘original’ triggered a massive direct-to-consumer advertising campaign by competitors such as GSK, coupled with an equally thorough promotion directed at physicians.⁶²⁴ The drive to cover the largest potential target population formed the basis for lobbying for off-label juvenile use.

As a result of the increasing number of product liability lawsuits contesting *Paroxetine*’s psychiatric ADRs, the submission of AG Spitzer contained allegations of

promotion of off-label use, especially when it constitutes a valid and more affordable alternative treatment).

⁶¹⁹ *People of the State of New York v. GSK*, case file, p. 9: “GSK has repeatedly misrepresented the safety and efficacy outcomes from its studies of paroxetine as a treatment for MDD in pediatric population to its employees who promote paroxetine to physicians [...] GSK Paxil Product Management stated ‘Paxil demonstrates REMARKABLE Efficacy and Safety in the treatment of adolescent depression’”.

⁶²⁰ As discussed in chapter V, the necessity of approving both Vioxx and Avandia in the first place was undermined by the presence of comparatively safe and already marketed therapeutic alternatives.

⁶²¹ See FDA Letter of Approval for NDA 18-936/S-064, retrievable from Prozac ‘Drug Approval Package’, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/18936S064_Prozac.cfm.

⁶²² On the impact of me-too drugs on the pharmaceutical market see the interesting study conducted by *Forbes* highlighting the tension between the negative impact on innovation and R&D for truly innovative treatments and the positive impact on competition and product prices: LaMattina J., “Impact of ‘Me-Too’ Drugs on Health Care Costs”, *Forbes*, January 2015.

⁶²³ See initial approved FDA labelling, retrievable from Zoloft ‘Drug Approval Package’, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/19-839S026_Zoloft.cfm.

⁶²⁴ As reported again in *People of the State of New York v. GSK* case file, pp. 9-10.

“repeated and consistent fraud” by GSK in concealing relevant data on Paxil’s potential ADRs related to suicidal trends in juvenile populations (as well as allegations of essential lack of effectiveness in those populations).⁶²⁵ Significantly, the submission referred specifically to failure to publish clinical trials outcomes which showed inconsistent results regarding the safety and efficacy of the treatment in juvenile populations.⁶²⁶ That allegation revolved around the fact that ‘off-label’ prescriptions require physicians to be in possession of all relevant information, short of which a producer would be misleading the practitioner and defrauding the final consumers.⁶²⁷ Spitzer’s lawsuit was therefore very much centred on the availability and accessibility of data relevant to safety assessment which GSK had failed to disclose to the FDA (and more obviously, in its advertising campaign to patients and physicians) while formally complying with NDA application requirements.⁶²⁸ The interesting feature of this case for the purposes of our study is that the AG’s submission did not venture into the merits of the Paxil-related ADRs, but focused rather on the inaccessibility of information aimed at guaranteeing the highest levels of relevant knowledge for the safety assessment of the drug (in this case by physicians rather than by the approving agency).

The impact of Spitzer’s lawsuit was remarkable. In August 2004 GSK agreed to settle the case, paying a sum of \$2.5 million and, more importantly, opening up its clinical trials register on an open access website.⁶²⁹ The terms of the settlement required GSK to publicise all trials related to safety and efficacy of *Paroxetine* in juvenile populations, but more generally to establish a company register providing summaries of all clinical research undertaken as of December 2000 for a period of 10 years⁶³⁰ – a requirement which facilitated important and measurable subsequent improvements in safety assessments of other products, as in the case of Avandia. This settlement also triggered a positive domino effect, with the prominent association Pharmaceutical Research and Manufacturers of

⁶²⁵ *Ibidem*, pp. 6-7.

⁶²⁶ It is noteworthy that the results of an investigation conducted by the UK MHRA revealed the existence of nine clinical trials conducted by GSK between 1994 and 2002, two of which showed no statistically significant benefit at all: Garland J.E., “Managing Adolescent Depression in the New Reality”, *British Columbia Medical Journal* 46, 2004.

⁶²⁷ See *People of the State of New York v. GSK* case file, pp. 6-16 and reported studies.

⁶²⁸ See Approval Letter for NDA 20-031/026, retrievable from Paxil ‘Drug Approval Package’, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/20-031S026_Paxil.cfm, and see *contra* the *People of the State of New York v. GSK* case file.

⁶²⁹ The trials data were made accessible in the GlaxoSmithKline Clinical Study Register at <http://www.gsk-clinicalstudyregister.com/>.

⁶³⁰ See the terms of the settlement in *People v. GlaxoSmithKline Plc*, WL 1932763, S.D.N.Y. 2004.

America (PhRMA – which, as discussed in chapter IV, is a voting member of ICH) promoting the adoption of similar registers among all major American manufacturers.⁶³¹ The dynamic of this case is of interest, with a line of product liability cases triggering a state lawsuit specifically focused on data availability, which managed to exert a significant impact on the dispute at hand but had much further reaching and more fundamental consequences. However, while the results of the GSK settlement are significant, their limits are just as evident. There are two clearly problematic aspects. On the one hand the time limitation built into the settlement (with full accessibility of company-sponsored trials granted for a period of 10 years, in other words the average duration of a single pre-approval process)⁶³² allows for only a restricted number of products to be investigated in full – as seen in chapter III, even in the case of *Rosiglitazone* access to pivotal trials submitted for marketing authorisation has not been possible, which perpetuates the uncertainty over the quality of data available for approval.⁶³³ On the other hand, a company-specific measure has inherently limited scope. While PhRMA did promote clinical trials registers within all major manufacturers, these have tended to be selective and incomplete as the trials reported are typically limited to voluntary post-marketing studies.⁶³⁴

A different account of court-imposed access to trials data emerges from a line of cases involving a series of decisions taken by the EMA. These decisions were specifically directed at requiring the release of clinical trials results from the pharmaceutical companies AbbVie and InterMune, each relative to one marketed product. It should be preliminarily observed that all three cases are of a particular nature. Unlike AG Spitzer's initiative in New York, they do not follow a strain of product liability litigation, but were rather triggered by a request for access to information filed by direct competitors of the marketing authorisation holders with the EMA. With two decisions adopted between late 2012 and early 2013,⁶³⁵ the agency took an executive decision to grant third parties (in this case the competitors) access to both non-clinical and clinical summaries of studies related

⁶³¹ See the initiative launched in October 2004 by PhRMA, the PhRMA Clinical Study Results Database, at <http://www.clinicalstudyresults.org/>, including data from Pfizer, Merck, Eli Lilly, GSK, and others.

⁶³² See the references in chapters II and III on timelines of product development and marketing.

⁶³³ As noted in chapter III, GSK responded to a direct request from the author for access to information in that case with a reference to the approved FDA label.

⁶³⁴ On a discussion of voluntary post-trials see chapter V.

⁶³⁵ See the final EMA decisions, Doc Ref EMA/748792/2012 of 14 January 2013, and Doc Ref EMA/24685/2013 of 15 January 2013.

to two pharmaceutical products that had been approved for marketing in 2007 and 2011.⁶³⁶ The legal grounds for EMA's decision to require data disclosure were to be found in the combined reading of articles 2 and 4(4) of Regulation 1049/2001⁶³⁷ on public access to documents. In the agency's opinion, the specific information requested fell within the category of documents which clearly need to be disclosed.

The marketing authorisation holders refused to deliver the relevant information, rebutting the EMA's position with the argument that clinical summaries should be covered by the exception laid down in article 4(2) of Regulation 1049/2001 – on the basis of which access to documents can be denied when the relevant information is of a confidential nature and no overriding public interest justifies disclosure (the exemption known as Confidential Business Information (CBI)).⁶³⁸ Rejecting this argument, the EMA proceeded to confirm access to the requested information on the basis that clinical studies should not be regarded as confidential information, and restating that as per article 4(4) “it is clear that the document shall [...] be disclosed”.⁶³⁹ The marketing authorisation holders then filed an appeal to the General Court (GC) which, in early 2013, reversed both the EMA's decisions.⁶⁴⁰ Supporting the view that the information requested by the interested third parties was indeed of a confidential nature, the President of the GC ordered the agency to refrain from disclosing the requested clinical studies reports.⁶⁴¹ As suggested in chapter III, these decisions *de facto* sanctioned, on the one hand, a wide discretionary power of industry in controlling the publication of data, and on the other hand, a strong tendency to uphold commercial confidentiality or individual privacy over transparency and access to information.⁶⁴²

⁶³⁶ AbbVie's Humira, see EMA EPAR Doc Ref EMA/178267/2015, and InterMune's Esbriet, see EMA EPAR Doc Ref EMA/64972/2015.

⁶³⁷ Regulation (EC) 1049/2001 of the European Parliament and of the Council regarding public access to European Parliament, Council and Commission documents OJ 2001 L 145/43.

⁶³⁸ Article 4.2 provides: “The institutions shall refuse access to a document where disclosure would undermine the protection of: — commercial interests of a natural or legal person, including intellectual property [...] unless there is an overriding public interest in disclosure”.

⁶³⁹ Case C-398/13 *EMA v. AbbVie Inc* §22 and Case C-390/13 *EMA v. InterMune Inc* §15 (both orders of the Vice-President of the Court).

⁶⁴⁰ Case T-44/13 Order of the President of the General Court, 29 April 2013, *AbbVie v. EMA*, OJ C 189; Case T73/13 Order of the President of the General Court, 25 April 2013, *InterMune v. EMA*, OJ C 189.

⁶⁴¹ *Ibidem*.

⁶⁴² See in particular the reasoning of the President of the GC as reported in the subsequent appeal Case C-390/13 *EMA v. InterMune Inc*, specifically at §§18-19 where the President rebuts EMA's change of policy in data disclosure.

Unsatisfied with the GC's decisions, the EMA filed three appeals at the CJEU, which, in two substantially identical cases, set aside the orders of the President of the GC.⁶⁴³ Interestingly, while acknowledging that the argument adopted by the marketing authorisation holders and accepted by the GC at first instance was erroneous, and that a consistent interpretation of the legislation and the relevant case law⁶⁴⁴ could not lead to the conclusion that clinical studies fall within the category of confidential information (a position at odds with the substantial inaccessibility of pivotal trials reported in chapter III), the court was unable to reach a final judgment, thus referring back the case to the GC to reassess the matter. As a result of this appeal, AbbVie promptly started a collaboration with the EMA which led to the end of the lawsuit, as the parties agreed on a set of redacted information to be made available. The agreement appears to satisfy the agency's requests on behalf of the interested third parties while protecting financially sensitive information, which remains with the marketing authorisation holder.⁶⁴⁵

This line of cases was discussed in chapters III and IV alongside the approval process for the new EU regulation on clinical trials,⁶⁴⁶ which places significant focus on clinical trials accessibility.⁶⁴⁷ It is hard to measure the concrete impact that the recalled access to trial information cases had in fostering that approval, but the timing is suggestive. The essential features of this legislation have been described earlier, but the key critical elements can be recalled briefly. First, the wording of the new requirements remains uncertain as regards the extent of the CBI exemptions,⁶⁴⁸ and only a close monitoring of actual enforcement practices will clarify if and to what extent such

⁶⁴³ The recalled Case C-398/13 *EMA v. AbbVie Inc* and Case C-390/13 *EMA v. InterMune Inc* .

⁶⁴⁴ The reasoning is based in particular on Order of the President in Case C-404/01 P(R) *Commission v. Euroalliances and Others*, ECR I-10367; Order of the President in Case C-445/00 R *Austria v. Council* [2001] ECR I-1461; Order of the President Case C-335/99 P(R) *HFB and Others v. Commission* ECR I-8705; and Case C-278/13 P(R) *Commission v. Pilkington Group* [2013] ECR I-00000.

⁶⁴⁵ REUTERS, "AbbVie drops legal action in EU drug secrecy case", 3 April 2014.

⁶⁴⁶ Regulation (EU) 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, OJ L 158, 27.05.2014, which was swiftly approved in April 2014, after two years' discussion.

⁶⁴⁷ Regulation (EU) 536/2014 arts. 80-82. See the discussion in chapters III and IV.

⁶⁴⁸ Toussaint B., "EU Clinical Trials Regulation", 381 *the Lancet* 9879, 2013, pp. 1719-1720; Götzsche PC., "Deficiencies in Proposed New EU Regulation of Clinical Trials", 345 *British Medical Journal*, e8522, 2012; Bonini S. et al., "Transparency and the European Medicines Agency – Sharing of Clinical Trial Data", *New England Journal of Medicine* 371, 2014; Strom B.L. et al., "Data Sharing, Year 1 – Access to Data from Industry-Sponsored Clinical Trials", *New England Journal of Medicine* 371, 2014.

provisions are effective.⁶⁴⁹ The new legislation is also non-applicable to products marketed before its entry into force,⁶⁵⁰ which suggests that the real impact of the new regulation will be perceivable for newly marketed drugs only in some 10 to 15 years from now. Finally, given the wording of article 1, the regulation applies to all clinical trials conducted “in the Union”,⁶⁵¹ implying that the issue of publication of trials conducted in third countries is yet to be legislatively addressed, except where special reporting duties are provided for.⁶⁵²

The conclusion of this first section is necessarily interlocutory. While non-liability cases in both the US (although, as discussed, the Spitzer case was triggered by previous lawsuits so the link exists indirectly) and the EU show that courts can have a major impact and a proactive role in fostering access to data, the risk is that interventions of this kind may remain sporadic as it is unclear what levels of follow-up can be guaranteed. The US settlement allowed for only temporary full data disclosure by one specific company for a decade. Moreover, the absence of directly affected parties (that is, damaged plaintiffs) in the proceedings reduces the desired diffuse bottom-up monitoring effect of court-based intervention. The EU cases for instance have been (at least partially) settled through the intermediary role of the EMA without direct involvement of the interested information seekers. The case law did however accelerate the approval of the new regulation, which is an important result, not to be understated despite the critiques raised above. In other words the examples raised in this section show how court cases can have a concrete positive impact on data accessibility (both directly and indirectly), with the caveat that a less episodic form of post-marketing control relying on courts requires the involvement of interested parties.

The following section goes therefore back to pure product liability cases. The goal is to examine the attitude of courts towards regulatory compliance, and their concept of knowledge availability, in order to determine whether a form of diffuse and continuous oversight can be provided via private liability claims.

⁶⁴⁹ See Rizzi M., “Simple Safe and Transparent? - Preliminary Reflections on the Adoption of a New EU Regulation on Clinical Trials”, *European Journal of Risk Regulation* 4, 2013, p. 534 ff.

⁶⁵⁰ See the discussion in chapter III.

⁶⁵¹ Regulation (EU) 536/2014 art. 1: “This Regulation applies to all clinical trials conducted in the Union”.

⁶⁵² See *ibidem*, arts. 42 and 53.

2. Enhancing assessment levels: beyond formal compliance

As suggested, the goal here is to show how the concept of regulatory compliance as accepted by the judiciaries in both the US and the EU allows for thorough review of the specific cases with which courts are confronted. The idea is to do so by recounting critical decisions that have contributed to defining the contemporary concepts of compliance and knowledge accessibility. While the discussion will focus on specific cases that have contributed to build product liability consolidated concepts, the section should be read keeping in mind the endgame of the thesis. Therefore, while focused on ‘classic’ issues of product liability, the section is meant to constitute a substantial brick in paving the way to the argument that courts can operate as reviewers of approval processes, and indirectly of the standards involved.

As already discussed in chapter VI, regulatory compliance is not a defence *per se*. While in the US the doctrine of preemption represented a vigorous attempt to introduce a *de facto* compliance defence, the reasoning in *Wyeth v. Levine* provides solid ground for rebuttal. The facts of that case are of interest to our study. The pharmaceutical product in question was *Promethazine* (commercially distributed by Wyeth as Phenergan).⁶⁵³ The medicine is an anti-nausea treatment that can be administered in several forms, particularly with two types of injection. The first, known as “IV-push”, requires the drug to be injected without intermediary measures directly into the patient’s circulatory system, while the second typology of injection is the “IV-drip” which injects the drug into a saline solution progressively ‘dripping’ through a catheter into the patient’s venous system.⁶⁵⁴ In the case at hand Ms Levine was injected with the “IV-push” method and as a result suffered a severe ADR leading to the amputation of her arm.⁶⁵⁵ What caused the initial ADR leading to the dramatic conclusion was the fact that Phenergan is a highly corrosive medicinal, and direct exposure of arterial blood during injection can cause gangrene.⁶⁵⁶ The claim that Ms Levine raised in the subsequent lawsuit brought against Wyeth was that warnings of potential dangers related to the “IV-push” method of administration were

⁶⁵³ See FDA Letter of Approval for NDA #007935 in ‘Drug Approval Package’, available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_Approval_History. A complete reconstruction of the case is provided by Goldberg R., *Medicinal Product Liability and Regulation*, Hart Publishing, 2013, p. 145 ff.

⁶⁵⁴ See the Phenergan original label from FDA ‘Drug Approval Package’.

⁶⁵⁵ *Wyeth v. Levine* 129 S Ct 1187, 2009, p. 1197.

⁶⁵⁶ *Ibidem*, p. 1191.

insufficient and understated in the drug labelling. Moreover (an essential point for us) she produced evidence suggesting that the intravenous injection of Phenergan should not have been allowed in the first place as unreasonably dangerous. The evidence reported unreasonable risk factors for both injection methods.⁶⁵⁷ After losing the case both at first instance and in the Supreme Court of Vermont,⁶⁵⁸ Wyeth took its challenge to the US Supreme Court. The appeal brought by the company revolved around the argument that a failure to warn claim at state level (as initiated and won by Ms Levine in Vermont) should be preempted by FDA's approval of the labelling.⁶⁵⁹

The Supreme Court's reasoning, briefly suggested in chapter VI, opens the door (or rather does not shut it) to a conception of regulatory compliance as a minimum standard, explicitly acknowledging the centrality of the role of courts in cases of this sort. Courts, the argument goes, have an essential role in promoting rather than ignoring the emergence of relevant assessment knowledge. Wyeth's appeal relied on the FDA's 2006 Preamble,⁶⁶⁰ alleging both the impossibility of modifying the labelling without prior FDA approval, and more generally the fact that state tort law requirements to improve the product label by reinforcing warnings on injection risks would defeat the objectives laid down by federal regulation on product labelling.⁶⁶¹ The Supreme Court rejected both arguments and it is worth reporting the rationale of the decision.

First, the impossibility by preemption appeal was dismissed on the ground that 'newly acquired information' can and should be integrated in drug labelling without the necessity of formal FDA approval. Additional information (in the form of more extensive warnings, or information pertaining to the dosage or use of a certain substance) should not be barred by the precondition of a federal approval when oriented at increasing product safety and ameliorating the safety of usage.⁶⁶² The Court's reasoning develops the idea that the accumulation of information over time implies that it is the manufacturer that must be primarily responsible for the adequacy of its labelling (not the regulator), and

⁶⁵⁷ *Ibidem*, pp. 1191-1192.

⁶⁵⁸ See *Levine v. Wyeth* 944 A 2d 179, 184 Vermont, 2006.

⁶⁵⁹ *Wyeth v. Levine* 129 S Ct 1187, 2009, p. 1194.

⁶⁶⁰ Preamble to FDA Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (24 January 2006, effective June 30, 2006) 21 C.F.R. Pts. 201, 314, 601.

⁶⁶¹ The two arguments are defined by the defendant as "impossibility by pre-emption" and "obstacles to federal regulation's objectives and purposes": *Wyeth v. Levine* 129 S Ct 1187, 2009, pp. 1204-1205.

⁶⁶² The Court refers to the consolidated FDA policy of traditionally relying on state court cases as a complement to federal regulation, *ibidem*, pp. 1201-1203.

that the ‘information available’ should encompass the widest possible spectrum, including evidence emerging in state courts. As a matter of fact, Ms Levine had presented evidence of significant risks related to the injection of Phenergan, as well as evidence of a series of previous clinical cases involving similar injuries deriving from the same form of treatment.⁶⁶³ The Court dismissed the argument that it was impossible to comply with both the FDA’s labelling approval regime and state tort law requiring amendments to the product’s label. To be receivable such an argument would have required proof that “the FDA would not have approved a change to the label”⁶⁶⁴ based on the new information – an assumption rightly considered unreasonable by the Court.

As for the second argument, relating to the danger of state tort law defeating the purpose of federal regulations, the Court explains that exclusive reliance on the FDA is not a sustainable way of promoting drug safety.⁶⁶⁵ We have discussed in chapters III and V that regulatory agencies suffer from a lack of financial resources necessary to accomplish the task of regulatory oversight (both pre- and post-marketing). In *Wyeth*, the Supreme Court expands upon the issue by recognising that the scarcity of resources available to the FDA is particularly affecting the post-marketing phase (in yet another implicit criticism of the PDUFA mechanism of funding), in which the agency alone is unable to effectively monitor all potential emerging risks.⁶⁶⁶ In this context, state tort law has to function as a complement to regulatory requirements in allowing the discovery of “unknown drug hazards” and in incentivising “manufacturers to disclose safety risks promptly”.⁶⁶⁷ With an apt choice of words, Richard Goldberg describes the role of tort law as a “catalyst”⁶⁶⁸ for the emergence of risk-related information.

The decision in *Wyeth* goes far in the direction suggested by this thesis that courts should perform a role in improving data quality. In particular, the concept that compliance alone is not a viable patent of safety is the metaphorical ‘key’ for a court to take a ‘hard look’ at approval processes – the idea that we shall further develop in chapter X. It must

⁶⁶³ *Ibidem*, p. 1197.

⁶⁶⁴ *Ibidem*, pp. 1197-1199.

⁶⁶⁵ *Ibidem*, p.1202.

⁶⁶⁶ *Ibidem*, and we refer to the discussion developed in chapter V on the limits of post-marketing surveillance resources.

⁶⁶⁷ *Ibidem*.

⁶⁶⁸ Goldberg R., *Medicinal Product Liability*, p. 149.

be reiterated however that the subsequent decision in *PLIVA Inc v. Mensing*⁶⁶⁹ is rather surprising, as by allowing preemption of state tort cases in lawsuits involving generic drugs, the Court contradicted the argument suggested above that information related to pharmaceutical risk is an incremental process for which manufacturers are primarily responsible.

In the European scenario, a ‘compliance defence’, although regularly advocated for by representatives of the industry,⁶⁷⁰ is not on the cards. As suggested in chapter VI the only defence explicitly mentioning regulatory requirements is the one provided by article 7(d) of the Product Liability Directive,⁶⁷¹ on the basis of which a producer will be shielded from liability where “the defect is due to compliance of the product with mandatory regulations issued by public authorities”. Short of that, regulatory compliance provides “strong evidence” that the product is not defective, but without freeing a producer from liability.⁶⁷² In other words the correct observance of a given standard, in product liability litigation, is strong but not conclusive evidence of a product’s safety. This is confirmed by the wording of article 25 of Directive 2001/83/EC on the basis of which a marketing authorisation “shall not affect the civil and criminal liability of the manufacturer and, where applicable, of the marketing authorisation holder”.⁶⁷³ More to the point of this chapter, it is important to determine the attitude of courts to improving the scientific data supporting safety assessments. Assuming that compliance is not an obstacle *per se*, the discussion should focus on the limits to the scope for introducing

⁶⁶⁹ *PLIVA Inc v. Mensing* 131 S Ct 2567, 2011 – the reasoning being that since a generic is by definition meant to be the ‘same’ as its original, for a manufacturer to modify the label without prior approval would violate the requirement of ‘sameness’ laid down by the relevant regulations.

⁶⁷⁰ Each Commission Report on product liability underlines the request from the pharmaceutical sector (typically through lobbying by EFPIA) to introduce a compliance defence into Directive 85/374/EEC: see again Commission Report, *First report on the application of Directive 85/374/EEC concerning liability for defective products* COM(1995) 617 final; Commission Report, *Second report on the application of Directive 85/374/EEC concerning liability for defective products* COM(2000) 893 final; Commission Report, *Third report on the application of Directive 85/374/EEC concerning liability for defective products* COM(2006) 496 final; Commission Report, *Fourth report on the application of Directive 85/374/EEC concerning liability for defective products* COM(2011) 547 final.

⁶⁷¹ Council Directive 85/374/EEC on the approximation of the laws and administrative provisions of the Member States concerning liability for defective products, OJ 1985 L 210, art. 7(d): “The producer shall not be liable as a result of this Directive if he proves: [...] (d) that the defect is due to compliance of the product with mandatory regulations issued by the public authorities”.

⁶⁷² For supplementary discussions on regulatory compliance see Goldberg R., *Medicinal Product Liability*; and Mildred M., “Pharmaceutical Products: The Relationship between Regulatory Approval and the Existence of a Defect”, *European Business Law Review* 6, 2007.

⁶⁷³ Council Directive 2001/83/EC on the Community Code relating to medicinal products for human use, OJ 2001, L 311/67, art. 25.

emerging scientific knowledge in court cases. In order to do so, an essential judgment that has inspired a number of subsequent decisions throughout the EU⁶⁷⁴ is the ECJ judgment in *Commission v. United Kingdom*.⁶⁷⁵ While we have identified in chapter VI some critical elements of it, we attempt here to give a more in-depth account of the reasoning of the ECJ, and to measure the impact of the decision as regards the ability of national courts to improve the quality of safety assessments.

The key element of the decision (largely based on the opinion delivered by Advocate General Giuseppe Tesaurò) concerns the concept of ‘the state of scientific knowledge’ and its reasonable accessibility. In particular, the Court sided with the AG’s opinion in defining the state of scientific knowledge as not commensurate with “the views expressed by the majority of learned opinion, but with the most advanced level of research which has been carried out at a given time”.⁶⁷⁶ The decision expands the argument by suggesting that even isolated opinions should be considered as an integral part of the scientific material to be assessed – since in the scientific community even minority opinions can rise to become widely accepted views.⁶⁷⁷ The Court is therefore leaning towards the highest level of inclusiveness, attenuated only by the requirement that such relevant knowledge has to be reasonably accessible. Here the argument for a construction of the role of courts as providers of higher data accessibility and quality requires a reading of the decision along the lines of what was initially suggested by Tesaurò. The Advocate General’s argument had posited that the reasonableness of accessibility should be measured against the level of knowledge that could be expected from the highest rank of expertise required in highly technical fields.⁶⁷⁸ Read in that light, the Court, while introducing a reasonableness requirement, decided the case in a way not dissimilar from the position taken almost fifteen years later in *Wyeth*, according to which manufacturers (which are to be considered as in possession of the highest levels of expertise in drug development) are ultimately responsible for the integration of emerging

⁶⁷⁴ Examples of cases based on the ECJ’s interpretation of art. 7(e) include in the UK, *A and Others v. National Blood Authority* (2001) 3 All ER 289 (HC), and in Italy, *Sentenza N. 1586/2006 del Tribunale di Brescia*, both addressing discoverability of risks in cases of infected blood transfusions.

⁶⁷⁵ Case C-300/95 *Commission of the European Communities v. United Kingdom of Great Britain and Northern Ireland* ECR 1997, I-02649.

⁶⁷⁶ Case C-300/95 *Commission v. United Kingdom*, Opinion of Advocate General Tesaurò, §21.

⁶⁷⁷ *Ibidem*, §22; and Goldberg R., *Medicinal Product Liability*, p. 174.

⁶⁷⁸ Case C-300/95 *Commission v. United Kingdom*, Opinion of Advocate General Tesaurò, §22.

knowledge in risk assessments:⁶⁷⁹ thus gearing up courts to function, again, as catalysts of knowledge production. While the reasonableness test does introduce limits to what can be expected from marketing authorisation holders, the example provided by the Court to define the boundaries of the test appears to limit its scope to truly borderline cases involving measurable barriers to access.⁶⁸⁰ The application of the Court's rationale in major tort cases involving toxic or biological products has been indeed leaning towards inclusiveness of emerging knowledge, as confirmed for example in the seminal UK case *A v. National Blood Authority*.⁶⁸¹

In a different but related area of European product liability, a strong signal confirming the Court's inclination towards accessibility and uncovering of scientific knowledge comes from the very recent CJEU decision in the *Novo Nordisk Pharma* case.⁶⁸² The court has held that national product-specific legislation imposing stricter liability mechanisms than the one provided by the Product Liability Directive is not affected by the Directive's regime as per article 13.⁶⁸³ While this was always the goal of the provision, the novelty consists of the fact that amendments posterior to the adoption of the Directive's regime are protected (and not only the legislation existing at the time the Directive was notified). This was of particular importance in the *Novo Nordisk Pharma* case, where the provision placed under scrutiny was a 2002 amendment to the *Arzneimittelgesetz* (AMG) introducing paragraphs 84(2) and 84a.⁶⁸⁴ The adoption of paragraph 84(2) introduced a presumption that, when the pharmaceutical product administered is generally capable of causing harm, the damage is caused by the product. Paragraph 84a introduced a consumer right to "require the manufacturer of a medicinal product to provide him with information

⁶⁷⁹ As previously discussed in the analysis of the essential p. 1202 of *Wyeth v. Levine*.

⁶⁸⁰ In §24 of his Opinion, Advocate General Tesauro illustrates the point by reference to the so called "Manchurian example" – his hypothesis revolves around research carried out and published in a Chinese academic journal (in Chinese) of a local university, with little circulation outside the region. The results of this research, even if published before the marketing of a product in Europe, would not be expected to be known by the manufacturer.

⁶⁸¹ *A and Others v. National Blood Authority* (2001) 3 All ER 289 (HC).

⁶⁸² Case C-310/13, *Novo Nordisk Pharma GmbH v. S.*, ECR 2014.

⁶⁸³ Council Directive 85/374/EEC on the approximation of the laws and administrative provisions of the Member States concerning liability for defective products, OJ 1985 L 210, art. 13: "This Directive shall not affect any rights which an injured person may have according to the rules of the law of contractual or non-contractual liability or a special liability system existing at the moment when this Directive is notified."

⁶⁸⁴ The presumption of a causal link referred to in paragraph 84(2) of the AMG and the right to information under paragraph 84a of the AMG were inserted into the AMG by the Law amending the legislation on compensation for damage (*Zweites Schadensersatzrechtsänderungsgesetz*) of 19 July 2002 (BGBl. 2002, p. 2674).

on the adverse effects of that product”⁶⁸⁵ when the facts of the case suggest that the product has caused damage. The CJEU recognised that the German legislation does not “undermine the effectiveness of the system of liability provided for under Directive 85/374”,⁶⁸⁶ but rather aims to eliminate or reduce the asymmetry of information between the manufacturer and the consumer, helping the latter to prove defectiveness and causation.⁶⁸⁷ The combination of the two suggested factors represents a powerful means of both consumer protection and judicial monitoring. It is quite significant that the CJEU, in sanctioning the strong German legislation, is endorsing a complementary approach. The case at hand involved Ms S. suffering ADRs related to the use of the anti-diabetes medicine known as Levemir⁶⁸⁸ marketed by Novo Nordisk. After suffering from lipodatrophy as a result of Levemir injections she required the manufacturer to provide her with full disclosure of side effects data pursuant to article 84 AMG.⁶⁸⁹ The decision of the CJEU in response to the initial refusal of Novo Nordisk (which had relied on the exact wording of the Product Liability Directive, from which the further obligation laid down in the AMG is absent) sets a promising tone for the future of pharmaceutical product liability litigation.

Whereas the attitude of US and EU courts towards access to and inclusion of relevant scientific knowledge in liability assessments has developed through time independently and in adjacent rather than juxtaposing fields, the conclusions are not dissimilar. The common theme emerging is that both judiciaries are in principle oriented towards an active role for liability law in considering and promoting the uncovering of scientific knowledge relevant to safety assessments. Regulatory compliance is interpreted as a strong element supporting claims of safety by marketing authorisation holders (what we have referred to as a ‘deferential’ approach). The challenge is to adjust the inclusive attitude to relevant information analysed in this chapter and to focus it on the weaknesses

⁶⁸⁵ Case C-310/13 *Novo Nordisk Pharma GmbH v. S.*, §29.

⁶⁸⁶ *Ibidem*, §30.

⁶⁸⁷ *Ibidem*, §32.

⁶⁸⁸ See EMA EPAR Doc Ref EMA/25588/2012.

⁶⁸⁹ AMG §84(2): “If, in the circumstances of an individual case, the medicinal product administered is capable of causing the damage, a presumption shall arise to the effect that the damage was caused by that medicinal product.[...]”.

AMG §84(a): “Where the facts suggest that a medicinal product has caused the damage, the injured party may require the pharmaceutical undertaking to provide him with information unless such information is unnecessary for the purposes of establishing whether damages may be claimed under Paragraph 84[...]”.

of regulatory outputs that emerged in chapters III and V. The ‘keys’ to open up the system – or more accurately the legal tools and interpretative inclinations – are already in place.

CHAPTER VIII

RELYING ON COURTS 2

PARTICIPATION IN COURTS – CAUSATION AND ACCESS DILEMMAS

We consider here the issue of access to justice in pharmaceutical cases to question the ability of courts to undertake the suggested complementary function. To discuss accessibility in a manner functional to the scheme of this thesis, the focus needs to be on two separate but very much mutually influential aspects. First, a complex issue that links the themes of data availability and access to justice is that of causation. The opening section of the chapter discusses the intricacies of reconstructing the causal links between the use of a pharmaceutical product and allegedly related harms to show how this essential step constitutes a major hurdle in accessing judicial oversight. The second section confronts the long-lasting debate opposing individual and collective redress. The question whether courts can constitute democratic agents seems to receive a more positive answer when mechanisms of collective redress are in place, because when individual cases are brought to court, the obstacle of causation can often be simply too burdensome for single parties.

1. Intricacies of causation: statistical evidence and individual reports

Causation in product liability claims, and especially in toxic products litigation, is without question the toughest burden placed on plaintiffs claiming compensation.⁶⁹⁰ A

⁶⁹⁰ Product liability and tort law literature in general is consistent on this point. See among others Owen D., Montgomery J., Davis M.J., *Products Liability and Safety*, Foundation Press, 2014; Goldberg R., *Medicinal Product Liability and Regulation*, Hart Publishing, 2013; Goldberg R. (ed.), *Perspectives on Causation*, Hart Publishing, 2011; Owen D.G., “Dangers in Prescription Drugs: Filling a Private Law Gap in the Health Care debate”, *Connecticut Law Review*, 42, 2010; Owen D., *Products liability law*, 2nd ed., Hornbook Series, Thomson West Group, 2008; Brüggemeier G., *Common Principles of Tort Law – A Prestatement of the Law*, BIICL, 2006; Cranor C., *Toxic Torts*

major complicating factor is the need to provide the court with two layers of proof – a double element which, with different characteristics, is substantially present across both the US and the EU. First, the product must be shown to be capable of causing the alleged harm *in general*, and secondly, a plaintiff must prove that the product in question did in fact cause the harm in the *specific* case.⁶⁹¹

An essential yet contentious tool used in courts to assess causal links is epidemiology. An epidemiological study is normally of significant statistical value as it analyses “the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems”.⁶⁹² Typically, what epidemiology allows for is the identification of patterns and trends in controlled populations – for instance a comparative analysis of the health conditions of a selected population exposed to a specific substance or environmental condition as opposed to a non-exposed control group. As recalled, in the realm of product liability litigation, a plaintiff must prove both general and specific causation. Therefore, in theory, since epidemiological studies are based on populations rather than single individuals, they serve very well the purpose of demonstrating general causation, as they are able to reveal statistical associations between a given pharmaceutical and a the alleged harm.⁶⁹³ However, the individual characteristics of the specific case normally require proof of specific causation to be constructed on more extensive information than statistical epidemiological data.⁶⁹⁴

– *Science, Law and the Possibility of Justice*, Cambridge University Press, 2006; Fairgrieve D., *Products Liability in Comparative Perspective*, Cambridge University Press, 2005; Goldberg R., Lonbay J., *Pharmaceutical Medicine, Biotechnology and European Law*, Cambridge University Press, 2001; Rabin R., *Perspectives on Tort Law*, ASPEN Publishers, 1995. This section is very much inspired by these works.

⁶⁹¹ Among others see Goldberg R., *Medicinal Product Liability and Regulation*; Owen D., *Products liability law*; Cranor C., *Toxic Torts*.

⁶⁹² The WHO defines epidemiology as “the study of the distribution and determinants of health-related states or events (including disease), and the application of this study to the control of diseases and other health problems. Various methods can be used to carry out epidemiological investigations: surveillance and descriptive studies can be used to study distribution; analytical studies are used to study determinants.” Available at <http://www.who.int/topics/epidemiology/en/>.

⁶⁹³ The most obvious example for our purposes is that of clinical trials – typical epidemiological studies showing associations between certain events (risks or benefits) and the controlled trial population.

⁶⁹⁴ The discussion below will analyse how corroborating non-statistical factors can be temporality, or previous medical history, time and duration of the exposure.

Interestingly, a significant trend in American litigation⁶⁹⁵ has been progressively reducing the gap between the two elements of causation, by bridging the concepts of legal and scientific proof. The generally accepted standard in civil litigation requires plaintiffs to prove their case on a balance of probabilities, and a result above 50% normally corroborates a causal link. This relatively clear-cut evidentiary attitude is not mirrored by any equivalent in the scientific world, where no fixed statistical criteria are considered universally sufficient to prove a causal link. The bridging initiative conducted by American courts attempts to merge the epidemiological concept of ‘relative risk’ with the necessity for a simplified judicial evaluation based on a balance of probability over 50%. The idea goes as follows: a relative risk is defined as the ratio of probability of occurrence of a given event (in the case of a medicinal product this can be the occurrence of an ADR) in a controlled group exposed to a substance, to the occurrence of the same event in a controlled non-exposed group. The idea developed by the American judiciary is that when the ratio is double, the general statistics can be relied on to prove specific causation.⁶⁹⁶

While extremely appealing for its relative simplification of an otherwise intricate issue, this approach, known as the ‘double risk theory’, is subject to a vast array of criticisms focused on the alleged arbitrariness of this judicial choice.⁶⁹⁷ Opposing voices point out the alleged substantial unreliability of the theory in cases where the biological mechanisms triggering a certain outcome are unknown,⁶⁹⁸ and therefore statistical evidence is little more than random if not adequately contextualised. This line of thinking, which has unsurprisingly found vigorous supporters in the reporters for the *Restatement (Third) of Torts*,⁶⁹⁹ rejects the use of statistical evidence for proof of specific causation. As recalled in chapter VI, the third *Restatement* adopts a very restrictive approach to pharmaceutical

⁶⁹⁵ See in particular the seminal case *Daubert v. Merrell Dow Pharmaceuticals Inc.* 116 S Ct 189, 1993, discussed in greater detail below for its impact on admissibility of individual reports; and *Merrell Dow Pharmaceuticals Inc. v. Havner* 953 SW 2d, Texas Supreme Court, 1997, and the follow-up *Merck & Co. Inc. v. Garza* 347 SW 3d, Texas Supreme Court, 2011.

⁶⁹⁶ As explicitly suggested in both *Daubert v. Merrell Dow* and *Merrell Dow v. Havner*.

⁶⁹⁷ See the discussion in Goldberg R., *Medicinal Product Liability*, p. 87 ff; also in particular see Berger M., “Upsetting the Balance between Adverse Interests: The Impact of the Supreme Court’s Trilogy on Expert Testimony in Toxic Tort Litigation”, *Law and Contemporary Problems* 64, 2001; Geistfeld M., “Scientific Uncertainty and Causation in Tort Law”, *Vanderbilt Law Review* 54, 2001.

⁶⁹⁸ See the argument on the substantial unreliability of purely statistical evidence in Stapleton J., “Factual Causation, Mesothelioma and Statistical Validity”, *Law Quarterly Review* 128, 2012.

⁶⁹⁹ See comment c to the *Restatement (Third) on Torts*, ALI, 2010.

liability claims, firmly based on reasonableness criteria, one of which entails that a causal link requires non-statistical evidence of individual circumstances leading to the damage.⁷⁰⁰

The simplicity of the double risk theory has however gained supporters across the Atlantic, and European courts have demonstrated an inclination towards the use of statistical and epidemiological evidence in the delicate exercise of proving causal links. In particular, a line of cases in the UK courts has thoroughly discussed the matter, albeit without reaching a clear conclusion. The arguments, which constitute an appropriate summary of the state of the debate, focus around two contrasting views. On the one hand an approach aimed at facilitating the plaintiff's task suggests that when a series of potential causes coexist in a given case, the plaintiff can prove the existence of a causal link by "showing that the tortious exposure has at least doubled the risk arising from the non-tortious cause or causes".⁷⁰¹ This view was expressed in the UK Court of Appeal by Smith LJ in the leading asbestos case *Sienkiewicz v. Greif (UK) Ltd*. In contrast with this attitude, in the Supreme Court's judgment in the same case, Lords Kerr and Rodger opined that epidemiological evidence is unreliable in assessing specific causation; general statistical proof simply cannot constitute the foundation upon which a judge can decide whether exposure to a certain substance actually caused the damage in an individual case.⁷⁰²

The heated judicial debate evident in the *Sienkiewicz* case must be confronted with the reality of a 'double risk theory' significantly gaining momentum in its "adjusted version".⁷⁰³ A middle-ground take on the dispute over the reliability of epidemiological evidence for proof of specific causation emerges from an older pharmaceutical product liability case in the US. In *Merrell Dow Pharmaceuticals Inc. v. Havner*,⁷⁰⁴ the Supreme Court of Texas anticipated the subsequent divide between advocates and detractors of the 'double risk theory' by stressing that epidemiological evidence can form a strong evidentiary basis for general causation, and also constitute an important building block of specific

⁷⁰⁰ See the discussion of section 6(c) of the *Restatement* on prescription drug liability in chapter VI.

⁷⁰¹ *Obiter dictum* from the opinion of Smith LJ in *Sienkiewicz v. Greif (UK) Ltd* [2009] EWCA Civ 1159, [2010] QB 370, §23.

⁷⁰² See *Sienkiewicz v. Greif (UK) Ltd* [2011] UKSC 10, [2011] 2 AC 229, §§162-163 (Lord Rodger) and §205 (Lord Kerr, concurring).

⁷⁰³ As analysed in three different jurisdictions by Goldberg R., "Using Scientific Evidence to Resolve Causation Problems in Product Liability: UK, US and French Experiences", in Goldberg R. (ed.), *Perspectives on Causation*; see also Stapleton J., "Factual Causation, Mesothelioma and Statistical Validity", and the essential contribution to the progress of the theory by Cranor C., *Toxic Torts*, p. 234 ff.

⁷⁰⁴ *Merrell Dow Pharmaceuticals Inc. v. Havner* 953 SW 2d, Texas Supreme Court, 1997.

causation. It does however need to be corroborated by supporting factors because epidemiology only illustrates an ‘association’ between product and harm, and causation requires evidence of additional individual elements.⁷⁰⁵ The factors to be considered are manifold, and relate for instance to the personal medical history of the patient.⁷⁰⁶ The key is not to mistake an association, showing in aggregate figures a statistical recurrence of a given event under given circumstances, with the more stringent concept of causation of the single event – as observed in abundant literature, the two do not necessarily coincide without further evidence.⁷⁰⁷ The *Sienkiewicz* UK Supreme Court judgment refers to *Merrell Dow* insofar as Lord Rodger stresses the necessity of evaluating non-statistical elements with particular attention to “temporality”.⁷⁰⁸ In his reasoning, temporality should factor in when a certain association between a pharmaceutical product and an ADR is established statistically, but the ADR could be caused by other factors. In this situation, the fact that the ADR occurred immediately after taking the medicine could, together with the epidemiological evidence, amount to proof of causation.⁷⁰⁹ While eloquently presented, this view fails to consider an important aspect. Temporality in pharmaceutical ADRs is seldom of an immediate nature except in the relatively rare case of some signature damages.⁷¹⁰ If temporality is to be a decisive factor, proof of causation in long-term ADRs would become increasingly difficult.

While epidemiological studies cannot possibly be the sole mechanism to prove a causal link (which would hinder access to justice in any case where an individual ADR is not yet supported by aggregate statistics, and nonetheless non-statistical evidence exists to support causation),⁷¹¹ we suggest that the greater reliance on statistical studies begun in the US and reaching Europe is generally to be welcomed as a positive development.⁷¹² It allows for complex cases to be heard and evaluated with adequate attention to contextual studies,

⁷⁰⁵ A concept refined by the same Court in *Merck & Co. Inc. v. Garza* 347 SW 3d, Texas Supreme Court, 2011.

⁷⁰⁶ *Ibidem*.

⁷⁰⁷ *Ibidem* and, in literature (to limit the reference to a restricted choice of legal scholarship without venturing into pure science), Goldberg R. (ed.), *Perspectives on Causation*; Stapleton J., “Factual Causation, Mesothelioma and Statistical Validity”; Geistfeld M., “Scientific Uncertainty and Causation in Tort Law”; and Cranor C., *Toxic Torts*, among others.

⁷⁰⁸ *Sienkiewicz v Greif*, §163 (Lord Rodger).

⁷⁰⁹ *Ibidem*.

⁷¹⁰ As discussed in chapters V and VII when presenting the difficulties of post-marketing surveillance mechanisms.

⁷¹¹ The major argument presented by Cranor in *Toxic Torts*, p. 234 ff.

⁷¹² *Contra* see in particular the strong stand taken by Stapleton J., “Factual Causation, Mesothelioma and Statistical Validity”; and the cautious approach of Goldberg R., *Medicinal Product Liability*.

while in time courts can progressively develop know-how in managing complex evidence of this sort.⁷¹³ The ‘double risk theory’ bears a certain risk of oversimplifying the relationship between scientific and legal proof, but when corroborated by supplementing factors (provided these are not too narrowly defined) statistical evidence does play a role in increasing the accessibility of judicial remedies.⁷¹⁴

Epidemiological studies are however not only potentially subject to criticism as tools in proving causation, as discussed above, but are simply not always available. In the absence of aggregate studies demonstrating statistical incidence, an alternative source of evidence lies in individual reports supporting causal reconstructions – which can take the form for example of compiled data from expert bodies, or expert testimonies. The abundance of reporting and expert witnessing in the US has triggered a rather restrictive response from the Supreme Court in a famous trilogy of cases.⁷¹⁵ The excesses of expert witnesses are a well-investigated weakening feature of the American legal system, where what is supposed to be a sporadic and case-specific activity has developed in time into a proper lucrative profession, often detached from reliable scientific methods.⁷¹⁶ In order to shield the legal system from what has been picturesquely defined as “junk science”,⁷¹⁷ the Supreme Court in *Daubert v. Merrell Dow Pharmaceuticals Inc.*⁷¹⁸ has developed a relatively stringent test for the acceptance of individual reports and expert testimonies. The case of *Daubert* revolved around the admissibility of scientific evidence based on the precedent in

⁷¹³ On the importance of educating courts about scientific evidence for solid assessments see the compelling arguments of Sheila Jasanoff in both *Science at the Bar – Law Science and Technology in America*, Harvard University Press, 1995 and later *Designs on Nature: Science and Democracy in Europe and the United States*, Princeton University Press, 2005. The argument for educated courts develops then into the pedagogical role such courts can take to supervise complex technical regulatory processes.

⁷¹⁴ It is significant to observe that the essential combination of statistical and non-statistical specific evidence is debated across Europe with similar results. For instance the French Cour de Cassation, in two judgments in short succession in 2009, has explained that even in the absence of general statistical studies supporting a liability claim, the court should take into due account all non-statistical individual-specific elements concordant in pointing to the use of a product (a vaccine in the case at hand) as the presumable cause of harm (and explaining why temporality alone cannot be a decisive factor): see Cassation Civile n 08-12781/2009, 25 Juin 2009 and Cassation Civile n 08-16097/2009, 24 Septembre 2009. These decisions have been however called into question by the subsequent Cassation Civile n 11-17738/2012, 26 Septembre 2012, where the court relied exclusively on the temporal proximity of the harmful event to establish a causal link.

⁷¹⁵ The recalled *Daubert v. Merrell Dow* case, and the following cases *General Electric Co. v. Joiner* 118 S Ct 512 Ed 508, 1997 and *Kumho Tire Co v. Carmichael* 119 S Ct 1167, 1999.

⁷¹⁶ See among others the excellent account of Shapin S, *The Scientific Life – A Moral History of a Late Moral Vocation*, The University of Chicago Press, 2008.

⁷¹⁷ An expression adopted after being used by Huber P., *Galileo’s Revenge: Junk Science in the Courtroom*, Basic Books, 1991.

⁷¹⁸ *Daubert v. Merrell Dow Pharmaceuticals Inc.* 116 S Ct 189, 1993.

Frye v. United States,⁷¹⁹ which had set the rather vague requirement that new scientific evidence or methods to be admissible should have “general acceptance” in the scientific community.⁷²⁰ In *Daubert* the Supreme Court pronounced a better-defined approach based on a series of criteria aimed at ensuring that expert testimonies should be “based on appropriate science pertinent to a legal decision”.⁷²¹ By this means the judge was assigned a central role in preliminarily assessing the soundness of both the evidence and the methodology.⁷²² The success of *Daubert* is measurable in the formulation of the revised Federal Rules of Evidence which now require that:⁷²³

A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:

- (a) the expert’s scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
- (b) the testimony is based on sufficient facts or data;
- (c) the testimony is the product of reliable principles and methods; and
- (d) the expert has reliably applied the principles and methods to the facts of the case

While answering a very rational necessity – that of eliminating low quality reports from admissible evidence – judges have upon occasion exercised this gatekeeping function in an overly restrictive way,⁷²⁴ rejecting not only evidence for the case at hand, but moving in the direction of general inadmissibility of individual case reports lacking support in aggregate data.⁷²⁵ While this has had an impact in ‘traditional tort cases’,⁷²⁶ examples from the National Vaccine Injury Compensation Program suggest that there is room for a more flexible (and actually more literal) interpretation of the *Daubert* rule.⁷²⁷ Vaccination

⁷¹⁹ *Frye v. United States* 293 F 1013 D.C. Cir. 1923.

⁷²⁰ *Ibidem*, p. 1014.

⁷²¹ *Daubert v. Merrell Dow* 116 S Ct 189, 1993, pp. 592-593.

⁷²² *Ibidem*. The Court enumerates a series of factors to be considered, in particular 1) the falsifiability of the theory; 2) peer review of the theory; 3) known or potential rate of error in the theory; and (4) acceptance of the theory within the scientific community.

⁷²³ Federal Rules of Evidence, Rule 702 – Testimony by Expert Witnesses, Pub. L. 93–595, §1, in the latest version of December 2011.

⁷²⁴ The critique is raised in particular by Cranor in *Toxic Torts*, p. 256 ff.

⁷²⁵ *Ibidem*.

⁷²⁶ *Ibidem* and see also Goldberg R., *Medicinal Product Liability*, p. 110; and Goldberg R., *Causation and Risk in the Law of Tort*, p. 163 ff.

⁷²⁷ Cranor reports how under the National Vaccine Injury Compensation Program, evidence rules allow for a more flexible use of case reports while formally abiding by *Daubert* standards: see *Toxic Torts*, p. 257.

compensation claims have been allowed to rely substantially on individual case reports in the absence of statistical epidemiologic studies – based on an evaluation of temporality and lack of alternative causal triggers.

This brief discussion of causation and admissibility paves the way for the following section, where issues of access to justice will be analysed through the dichotomy between individual and collective redress. What emerges from this first section is that courts are struggling to reconcile the disparate ideas of legal and scientific proof. While the US has battled with judicial ‘junk science’ and opted for restrictive approaches to individual reports (although this seems to be attenuated at least in vaccination cases, which could open the door to a more inclusive attitude for medicinal products), what we observe is a general trend common to the US and the EU of allowing greater reliance on statistical methods of proof – at least in the form of a growing inclination towards aggregate epidemiological statistics when available. As will be discussed in the following section, this has the effect of simplifying proof of causation to a greater extent in collective redress cases than it does in individual ones. A significant alternative is that offered by the German *Arzneimittelgesetz* (AMG), discussed in chapter VII. The AMG in section 84(2)⁷²⁸ creates a presumption of specific causation when the product is shown to be capable of causing the damage in general (a proof typically relying on epidemiological studies). The presumption is rebuttable by the defendant who is however required to disclose any and all relevant information in his possession relating to the contested ADR. This scheme will be further discussed in the next section.

Beyond pharmaceutical products, the CJEU has very recently confronted the issue of causation in related fields, in particular medical devices, in the *Boston Scientific* cases.⁷²⁹ Here the court, on the one hand, creates a presumption of defectiveness where products belonging to the same group or production series have potential defects – in which case the product under specific scrutiny “may be classified as defective without there being any

⁷²⁸ AMG §84(2): “If, in the circumstances of an individual case, the medicinal product administered is capable of causing the damage, a presumption shall arise to the effect that the damage was caused by that medicinal product[...]”.

⁷²⁹ Cases C-503/13 *Boston Scientific Medizintechnik GmbH v AOK Sachsen-Anhalt - Die Gesundheitskasse* and C-504/13 *Boston Scientific Medizintechnik GmbH v Betriebskrankenkasse RWE* ECR 2015; for another recent decision on causation, in the field of cartel damages, see Case C-557/12 *Kone AG v ÖBB-Infrastruktur AG* ECR 2014.

need to establish that that product has such a defect”,⁷³⁰ thus considerably alleviating the victim’s burden of proof. On the other hand, corroborating a favourable interpretation of causal requirements for claimants suffering from injuries in health-product related cases, the Court broadens the spectrum of damages imputable to the manufacturer to cover collateral damages such as those deriving from surgical operation for the replacement of a defective medical device.⁷³¹

2. Participation in litigation: different shades of access to justice

The issue of causation is closely linked to the general theme of accessibility of the court system, which we touch upon to evaluate the surrogate participatory function of the judiciary. The argument here is that despite substantial criticisms culminating in a judicially and politically hostile attitude, the US model of class actions still represents the best option to guarantee accessibility to courts and, in turn, a diffuse form of bottom-up control of regulatory practices through litigation. It has been observed that American courts and governments have been less and less inclined to promote class actions for numerous reasons.⁷³² First, the relatively easy criteria laid down by law in 1966⁷³³ triggered as of the 1980s a rush to litigation in mass torts cases, especially those involving asbestos or Agent Orange.⁷³⁴ While saluted positively as an effective means of ensuring plaintiffs’ compensation and creating a strong deterrent for potential mass tortfeasors, the pattern of class action lawsuits turned rapidly in the 1990s into a relatively easy means of obtaining multi-million dollar settlements.⁷³⁵ The simple creation and certification of a class became quickly a compelling threat for defendants to the extent that class certification became the passport to big settlements accepted by defendants to avoid the prospect of financially devastating jury judgments.⁷³⁶ After important court decisions tackling the issue by

⁷³⁰ *Ibidem* §43.

⁷³¹ *Ibidem* §55.

⁷³² See for a full account the excellent piece by Klonoff R.H., “The Decline of Class Actions”, *Washington University Law Review* 90, 2013, on which this section relies substantially.

⁷³³ Federal Rules of Civil Procedure, Rule 23 – Class Actions, Pub. L. 109-2 §7 in the original version of 1966.

⁷³⁴ See Klonoff R.H., “The Decline of Class Actions”, p. 736, where reference is made to the asbestos and Agent Orange cases *In re Sch. Asbestos Litigation* 789 F.2d 996 3d Cir., 1986, and *In re “Agent Orange” Product Liability Litigation* 818 F.2d 145 2d Cir., 1987.

⁷³⁵ *Ibidem*, p. 736; see the important US Senate Report, No. 109-14, 2005.

⁷³⁶ *Ibidem*; the Senate Report refers to “Judicial blackmail forces settlements of frivolous cases”, p. 20.

allowing class certification review by appellate courts,⁷³⁷ a statutory intervention introduced the new rule 23(f) of the Federal Rules of Civil Procedure (FRCP), which formally vested courts of appeals with the power of permitting appeals “from an order of a district court granting or denying class action certification”.⁷³⁸ Establishing clear criteria for permitting appeals and certification reviews has been a prolonged and consuming exercise that courts have engaged with for over a decade.⁷³⁹ While a full reconstruction of each argument goes well beyond the scope of this chapter, the net result has been universally accepted as being fundamentally favourable to defendants, restricting significantly the margin of manoeuvre for plaintiffs to get a class certified.⁷⁴⁰ As observed by Robert Klonoff, while FRCP applied only to federal cases, “the most egregious examples of class action abuse had occurred in the state courts”.⁷⁴¹ The response to this incongruence came in 2005 with the adoption of the controversial Class Action Fairness Act (CAFA), which contains detailed procedures ensuring that most cases involving class certification can be removed from state courts to federal circuits.⁷⁴² The requirements permit *de facto* the removal of any case involving an amount of \$5 million or more, with little regard to diversity between plaintiffs and defendants or state of origin criteria.⁷⁴³

The new legislation, coupled with a stringent reading of rule 23(f), has been constructed in such a way that now, since a 2001 decision by the Seventh Circuit,⁷⁴⁴ the merits of a case are often reached at the preliminary class certification stage – thus erecting an initial threshold often fatal to aggregate plaintiffs seeking certification.⁷⁴⁵ What is interesting however is that while the general trend is indisputably towards a severe limitation in the scope of class actions, none of the defining cases contributing to this progressive restriction involved pharmaceutical product litigation. The most notable intervention on admissibility of evidence regarding pharmaceuticals remains the recalled

⁷³⁷ *In re Rhone-Poulenc Rorer Inc.* 51 F.3d 1293 7th Cir., 1995.

⁷³⁸ Federal Rules of Civil Procedure, rule 23(f), 1998.

⁷³⁹ See Klonoff R.H., “The Decline of Class Actions”, p. 741 ff.

⁷⁴⁰ *Ibidem*: see in particular Appendix A: Outcomes of Cases Appealed under Rule 23(f) between November 1998 and May 2012.

⁷⁴¹ *Ibidem*, p. 743.

⁷⁴² Class Action Fairness Act Pub. L. 109-2 §4, 2005: see comments by Issacharoff S., Nagareda R., “Class Settlements under Attack”, *University of Pennsylvania Law Review* 156, 2008, and Karabell J., “The Implementation of ‘Balanced Diversity’ Through the Class Action Fairness Act”, *New York University Law Review* 84, 2009.

⁷⁴³ See the full amendments brought by the CAFA as regards diversity of citizenship, amount in controversy, and costs in 28 U.S.C. § 1453(b) (2006); and 28 U.S.C. § 1332(d)(2), (d)(5)(B).

⁷⁴⁴ *Szabo v. Bridgeport Machines, Inc.* 249 F.3d 672 7th Cir., 2001.

⁷⁴⁵ See Klonoff R.H., “The Decline of Class Actions”, p. 747 ff.

Daubert case, which had a different aim.

To obtain a class certification plaintiffs must now satisfy the criteria laid down in rule 23(a) and (b) of the FRCP, in particular the main requirements enumerated in subsection (a): *numerosity* (that is, a minimum number of members which would make it impractical to nominate them separately as independent parties), *commonality* (which refers to a common legal and factual ground implying that a single solution covers the full class), *typicality* (meaning that the claims of the named parties are typical to all class members), and *adequacy* (requiring named plaintiffs to represent the interests of the entire class).⁷⁴⁶ This construction is very much functional in a pharmaceutical case involving epidemiological evidence. In particular, while the epidemiological evidence constitutes proof of general causation, the aggregation of class members based on the criterion of commonality represents a preliminary consolidation of specific causation evidence. By recognising patterns among class members associated by similar factual elements (for instance exposure to a certain substance, time of exposure, nature of the ADR, severity of the ADR, time lapsing between exposure and harmful event), the class certification process creates the basis for greater reliability of the evidence and stronger proof of causal links – in other words, the very constitution of the class based on commonalities adds specificity to general statistics.⁷⁴⁷ In this sense it is not entirely surprising that while severely criticised and facing limitations in a vast range of fields, class actions are still a lively feature of American pharmaceutical litigation. Several cases posterior to the adoption of both rule 23(f) and the CAFA bear testimony to this – Avandia, to come back to one of the cases analysed in chapter V,⁷⁴⁸ is a major but not isolated example.⁷⁴⁹ The recent study by Klonoff on “The Decline of Class Actions”, while very thorough in compiling restrictive case law rejecting class certifications, does not enumerate a single

⁷⁴⁶ Rule 23(a): “Prerequisites. One or more members of a class may sue or be sued as representative parties on behalf of all members only if:

- (1) the class is so numerous that joinder of all members is impracticable;
- (2) there are questions of law or fact common to the class;
- (3) the claims or defenses of the representative parties are typical of the claims or defenses of the class; and
- (4) the representative parties will fairly and adequately protect the interests of the class.”

⁷⁴⁷ As per the criteria elaborated by the Texas Supreme Court in *Merrell Dow v. Havner* and *Merck*, see the discussion *supra*.

⁷⁴⁸ See the account of the multi-billion settlements agreed upon by GSK to settle Avandia-related multi-state class actions provided by the non-profit drug information network Drug Watch International, available at <http://www.drugwatch.com/avandia/lawsuit.php>.

⁷⁴⁹ See the regularly updated database of ongoing drug-related class actions provided by Drug Watch International, available at <http://www.drugwatch.com/lawsuits/>.

drug case (except *In Re Copley Pharmaceutical, Inc.*,⁷⁵⁰ which preceded the adoption of rule 23(f), and was resolved by the Wyoming district court through a decision that the class certification had been appropriate under the circumstances). Why does pharmaceutical product liability class litigation appear resistant in an otherwise hostile context? An explanation based on our previous discussion of causation suggests that the very nature of a class, which invites the uncovering of statistical data in a closed and controlled group, is the most effective corroborating factor of general statistical evidence. The anchoring of pharmaceutical class actions to the *commonality* requirement seems capable of protecting them from the restrictive interpretation recently adopted by the Supreme Court in the contentious case of *Wal-Mart Stores, Inc. v. Dukes*.⁷⁵¹ In this judgment the Supreme Court explained that the common legal or factual claim should be “capable of class-wide resolution”, which implies that “determination of its truth or falsity will resolve an issue that is central to the validity of each one of the claims in one stroke”⁷⁵² – a natural feature of claims related to ADRs.⁷⁵³

Despite the strong critiques raised against the mechanism of US class actions and the rather vehement attacks this mechanism has suffered from limiting Supreme Court decisions, its value in enabling victims to obtain a form of judicial remedy is still recognized and argued for. In particular John Coffee, in a very recent study, makes a compelling case for class actions with the goal of maintaining, provided a series of necessary reforms are implemented, the crucial aspect of what he defines ‘entrepreneurial litigation’ – the safeguard of meritorious claims that would not be asserted in the absence of class mechanisms.⁷⁵⁴ More so, the author ventures into the possibility for the model of a “Private Attorney General” to be exported globally.⁷⁵⁵ Without entering into the details of such a complex proposal, it is worth noting the resilience that the concept of representative lawsuits has maintained over decades of controversial operation.

⁷⁵⁰ *In Re Copley Pharmaceutical, Inc* 161 F.R.D. 456 D. Wyo., 1995, cited in Klonoff R.H., “The Decline of Class Actions”, p. 797.

⁷⁵¹ *Wal-Mart Stores, Inc. v. Dukes* 131 S. Ct. 2541, 2011; see the thorough discussion in Klonoff R.H., “The Decline of Class Actions”, p. 775 ff.

⁷⁵² *Wal-Mart Stores, Inc. v. Dukes*, p. 2548.

⁷⁵³ This is not to say that all ADRs have the necessary commonality: for example, while a class action regarding cardiovascular ADRs could absorb all patients suffering from that category of side effect, a claim arising from, for example, hepatotoxicity would not be covered.

⁷⁵⁴ Coffee J. Jr, *Entrepreneurial Litigation – Its Rise Fall and Future*, Harvard University Press, 2015; see in particular parts Two ‘The Rise of the Entrepreneurial Litigator’ and Three ‘The Search for Reform’.

⁷⁵⁵ *Ibidem*, part Four ‘The Future’.

Identifying class actions as the best fitted means of ensuring access to justice in pharmaceutical litigation entails the obvious setback that the European scenario does not offer equivalents to the American model. The reasons are to be found in the diverse legal traditions of European states, and it is noteworthy that the contemporary debate is still very much anchored to traditional views in this regard.⁷⁵⁶ The major and most persistent objection to class actions, similar to what triggered the restrictive trend observed in the US, is the risk of excessive and uncontrolled litigation outbreaks.⁷⁵⁷ While the concern is legitimate as the US experience shows, it is also true that, as briefly suggested, careful regulation and adequate judicial oversight can significantly reduce the issue. That notwithstanding, the European version of collective redress is a significantly different phenomenon, with reduced impact on civil litigation. For example, Italy and Germany do have national laws on collective redress mechanisms.⁷⁵⁸ However the German legislation is limited to litigation involving capital markets, excluding other civil law types of claims, while the Italian law offers an intermediary service whereby a consumer association can start a lawsuit on behalf of interest groups, but the success of this venture has been so far limited.⁷⁵⁹ An equivalent of the US mechanism based on careful construction of a class sharing key common features and, by virtue of those commonalities, enhancing the statistical significance of individual events with a view to proof of specific causation does not exist.

In a series of studies dedicated to the state of collective redress in Europe, Christopher Hodges identifies a number of reasons for the European court systems not to venture into a US-style class action mechanism. These concerns are focused on the high transaction costs of litigation schemes, which in turn should suggest a preference for more traditionally European solutions characterised by the presence of public bodies monitoring

⁷⁵⁶ As suggested below, the American model of class actions is consistently very negatively evaluated: see for example the Commission Recommendations 2013/396/EU on common principles for injunctive and compensatory collective redress mechanisms in the Member States concerning violations of rights granted under Union Law, OJ 2013 L 201/60; Hodges C., “Collective Redress in Europe: The New Model”, *Civil Justice Quarterly* 7, 2010; Hodges C., *The Reform of Class and Representative Actions in European Legal Systems*, Hart Publishing, 2008.

⁷⁵⁷ See below on the Commission Recommendations 2013/396.

⁷⁵⁸ Legge 244 del 24 Dicembre 2007, and Kapitalanleger - Musterverfahrensgesetz (KapMuG) of 1st November 2005.

⁷⁵⁹ For a helpful practitioner’s account of the very limited success of the Italian collective action legislation, see Unnia F., “Le class action non superano lo scoglio dell’ammissibilità”, *IusLetter*, 25 November 2013, available at <http://iusletter.com/le-class-action-non-superano-lo-scoglio-dellammissibilita/>.

compensation mechanisms.⁷⁶⁰ Unsurprisingly, the current European trend goes very much in the direction of compensatory alternative dispute resolution schemes, which have been defined by the Directorate General for Health and Consumers Affairs (DG SANCO) as the “favoured approach for consumer redress at EU level”.⁷⁶¹ This policy orientation culminated in the adoption of the alternative dispute resolution Directive 2013/11.⁷⁶² The limiting feature of a system purely based on alternative dispute resolution is obviously that the post-factum control exercisable by a court gets lost. But more to the point of our analysis, the mechanism provided by the Directive is limited to “contractual obligations stemming from sales contracts or service contracts”,⁷⁶³ and article 2.2(h) establishes an explicit exception for prescription, dispensation and provision of medicinal products⁷⁶⁴ – limiting the potential applicability of the Directive to non-prescription medicines. Aware of the limits of the current approach, the Commission has released a series of non-binding recommendations⁷⁶⁵ on the adoption of collective redress mechanisms by Member States. While encouraging MSs to adopt collective redress schemes, the authors of these recommendations explicitly suggest that the desired result is “a balanced approach to improve access to justice for citizens while avoiding a US-style system of class actions and the risk of frivolous claims and abusive litigation”.⁷⁶⁶ The initiative is still relatively confined, as national legislatures are generally yet to incorporate the Commission’s recommendations. But the issue of access to justice is recognised, and this should be a factor in future legislative developments. The area of consumer protection in particular is repeatedly identified as necessitating adequate enforcement mechanisms for

⁷⁶⁰ Hodges C., *The Reform of Class and Representative Actions in European Legal Systems*, in particular chapters 2 and 4. See for a law and economics perspective Backhaus J., Cassone A., Ramello G. (eds), *The Law and Economics of Class Actions in Europe – Lessons from America*, Edward Elgar, 2012.

⁷⁶¹ See Hodges C., “Developments in Collective Redress in the European Union and United Kingdom 2010”, in *Global Class Action Exchange*, available at <http://globalclassactions.stanford.edu/taxonomy/term/105>, pp. 4-5.

⁷⁶² Directive 2013/11/EU of the European Parliament and the Council on alternative dispute resolution for consumer disputes and amending Regulation (EC) No 2006/2004 and Directive 2009/22/EC (Directive on consumer ADR) OJ 2013 L 165/63.

⁷⁶³ Directive 2013/11 art. 2.1.

⁷⁶⁴ Directive 2013/11 art. 2.2(h): “This Directive shall not apply to [...] (h) health services provided by health professionals to patients to assess, maintain or restore their state of health, including the prescription, dispensation and provision of medicinal products and medical devices”.

⁷⁶⁵ Commission Recommendations 2013/396/EU.

⁷⁶⁶ Commission Press Release of 11 June 2013, ‘Commission recommends Member States to have collective redress mechanisms in place to ensure effective access to justice’; see the contribution by Nuyts A., Hatzimihail N. (eds), *Cross-Border Class Actions: The European Way*, Sellier, 2013., and the recent review by Hodges C., “Cross-Border Class Actions: The European Way, edited by Arnaud Nuyts and Nikitas Hatzimihail (Munich: Sellier, 2013”, *Common Market Law Review* 52, 2015.

effective protection of consumer rights.⁷⁶⁷

While the current European model revolves around alternative dispute resolution and cautious initiatives encouraging the adoption of national legislation on collective redress, the issue of access to justice, in the sense of access to public courts, remains a difficult one. In a complex analysis of national legal tradition confronted with EU tendencies, Hans-W. Micklitz has developed the idea of “access justice” in the EU. Interestingly he identifies it as conceptually linked to the common law notion of equity – access, in this reconstruction, is the key to mitigating not the rigidities and iniquities of the common law, but the failures of the EU regulatory schemes.⁷⁶⁸ But how does EU law allow for the “*realistic* opportunity” to obtain compensation and enforcement of one’s rights? Certainly the adoption of Directive 2013/11 is a step forward from a situation in which consumer protection was suffering from limited access tools to ensure consumer rights enforcement.⁷⁶⁹ However, reliance on alternative dispute resolution mechanisms (such as conciliation or mediation) is, as already stated, insufficient in a field (such as pharmaceutical regulation) which stands in need of external oversight (possibly, reliance on an ombudsman could be helpful) – not to mention that the Directive is expressly non-applicable to prescription medicines, which are inherently more potentially harmful than non-prescription ones. Beyond the limiting effect of the exception in article 2.2(h), the issue is that compensation is only one side of the problem. To effectively tackle deterrence on the one hand and, more to the point, regulatory oversight on the other hand, access to justice in its more traditional sense is an inescapable issue. Obstacles to accessing the judicial system – setting aside in this context economic responses such as contingency fees which have been repeatedly ostracised by both commentators and EU institutions – need careful reflection at least around issues of causation. In a study on the “Common Principles of Tort Law”, Gert Brüggemeier correctly identified that toxic tort litigation in Europe suffers from a double handicap compared to the US: a substantive and a procedural one.⁷⁷⁰ The substantive obstacle consists of the difficulties in proving medical causation that have been described in the previous section – for the proof of which

⁷⁶⁷ Commission Recommendations 2013/396/EU and Commission, ‘Green Paper on Consumer Protection’, COM(2008)794.

⁷⁶⁸ Micklitz H.-W., “Social Justice and Access Justice in Private Law”, *EUI Working Paper Law* 2011/02, p. 23.

⁷⁶⁹ *Ibidem*, pp. 23-27.

⁷⁷⁰ Brüggemeier G., *Common Principles of Tort Law – A Prestatement of the Law*, pp. 259-263.

individual cases tend to be ill-suited. On the other hand there is a procedural problem in that the absence of a European class action mechanism often produces serial cases with lower chances of success and higher individual burdens – not to mention, ironically, the elevated transaction costs of multiple lawsuits.⁷⁷¹ Correctly, the author suggests that “the American law in this area is more developed”.⁷⁷²

The conclusion of this chapter is necessarily a composite one. Access to justice in this area is not only linked to the traditionally identified financial and economic burdens of the European court system compared to the American one (the classic example being the presence in the US of contingency fees, a clearly litigation-friendly mechanism).⁷⁷³ A more complex reading of the theme links access to courts with proof of causation, and we have argued that the class-identification mechanism set out in rule 23 of the FRCP actually appears to create a virtuous circle. Indeed, the aggregation of individuals sharing a given factual *commonality* (ADRs in pharmaceutical cases) allows on the one hand the construction of a class with the single goal of common resolution of a common problem, while contributing from the pre-trial phase to building the evidentiary foundations of both general and specific causation. Absent similar mechanisms in the EU, access to justice maintains its causal difficulties. The comparatively inferior number of cases litigated in the EU as against the US is unsurprising given that venturing upon an individual product liability claim necessitating complex health-related evaluations is still, to put it a bit dramatically, an act of courage. Of course individual cases do go to court, as discussed both in chapter VII and in the previous section, and when they do, decisions may be reached with significant impact – for example regarding the emergence of scientific knowledge, as suggested by the discussion in chapter VII. It is also true that, in theory, high numbers are not essential for the purpose of relying on courts for the review of regulatory standards (the claim of the thesis to be developed in chapter X). However, when it comes to assessing the viability of courts in the role of democratically accessible agents, the current scenario is less than optimal. How the EU will respond to the challenge of access to justice in a field where cooperation with the US is close and bound to get

⁷⁷¹ *Ibidem*, p. 261.

⁷⁷² *Ibidem*.

⁷⁷³ See again Reimann M., “Liability for Defective Products at the Beginning of the 21st Century: Emergence of a Worldwide Standard?”, *The American Journal of Comparative Law* 51, 2003 – but somewhat *contra* see Kelemen R.D., “Eurolegalism and Democracy”, *Journal of Common Market Studies* 50, 2012. See also the brief account in chapter VI of the element of the European form of *de facto* preemption.

closer is an issue to be monitored in the years to come. The impression is that, at the moment, the US court system is still better equipped to provide the ‘judicial governance’ and the diffuse ‘bottom-up’ oversight of regulatory mechanisms suggested in the opening remark above and in the first chapter.

We can however conclude with two positive observations for the EU. First, national experiences can reveal alternative means of facilitating individuals in court claims. The German legislation recently endorsed by the CJEU is an interesting alternative to a class action method. In the presence of epidemiological evidence demonstrating that the product can cause harm in general, the law creates a rebuttable presumption that it did in fact cause harm in the specific case. Secondly, the relative increase in litigation figures demonstrated by the succession of Commission product liability reports⁷⁷⁴ over 20 years, combined with the recent recommendations to MSs on the adoption of collective redress mechanisms, are signals that the debate is alive – access to justice, interpreted as access to public courts and not only to alternative dispute resolution schemes, is viewed as an issue requiring attention. It is possibly more than a significant coincidence that this slow but steady increase in litigation demand follows in time the described evolution of regulatory schemes and their pressure points.

⁷⁷⁴ The trend is visible, as discussed in chapters VI and VII, in Commission Report, *First report on the application of Directive 85/374/EEC concerning liability for defective products* COM(1995) 617 final; Commission Report, *Second report on the application of Directive 85/374/EEC concerning liability for defective products* COM(2000) 893 final; Commission Report, *Third report on the application of Directive 85/374/EEC concerning liability for defective products* COM(2006) 496 final; Commission Report, *Fourth report on the application of Directive 85/374/EEC concerning liability for defective products* COM(2011) 547 final.

CHAPTER IX

RELYING ON COURTS 3

COURTS AND LITIGATION OUTPUT: ADEQUATE COMPLEMENTS?

This third and final chapter on the role of the judiciary and litigation in complementing regulatory processes touches upon the complex issue of the adequacy and reliability of litigation outcomes in a complex field such as pharmaceutical safety, and provides an opportunity to reassemble and evaluate the themes emerging in the previous chapters.

1. Two major arguments *contra* judicial involvement

It is worth recalling the classic arguments against judicial oversight of the outputs of technical regulatory processes mentioned in the Introduction. These are essentially two. First, it is argued that courts are unprepared to tackle difficult scientific issues, and should therefore defer to the outcome of regulatory assessments (if the possibility of review is to be entertained at all). The second argument is that litigation is an inefficient means of regulatory oversight because of the inherently high transaction costs and prolonged timelines involved. Correlated to both, there is a more general argument that product liability cases do not provide any measurable social benefit, and that a system based on regulatory minimum standards and self-regulatory market incentives is best suited for the governance of product safety at large.

This chapter addresses the arguments in turn, with no ambition to rebut them in a definitive fashion, but rather by suggesting pointers to the adequacy on the one hand and fruitfulness on the other of court cases in the pharmaceutical context. To this end, the following section briefly analyses how the alleged technical incompetence of courts can be overcome in practice by their ability to make important value-based judgment calls in the

face of uncertainty – with impacts and implications possibly reaching beyond the boundaries of the single case at hand. This has been discussed previously when addressing causation; here the analysis reassesses that discussion to advocate for the substantive adequacy of judicial decision-making.

The final section revisits a series of cases considered in previous chapters which underpin the claim that fortuity of risk discovery and delays in swiftly addressing safety issues upon their discovery are structural to the regulatory system. Experience from these cases points to the existence of an identifiable and non-negligible trend where, in the presence of emerging safety issues, the regulatory system takes action *as a consequence* of litigation – either after the case has started or after it has been decided or settled. Administrative actions such as suspension of marketing authorisation or re-labelling of products have often lagged behind private litigation initiatives. This failure (episodic but recurrent) to act upon safety issues, analysed in chapter V, makes room for the argument that courts can and are in fact exercising an important surrogate post-marketing surveillance function. The observations provided in the following pages should pave the way for the concluding chapter and for the argument that the patterns highlighted throughout this thesis call for a renewed role of courts in tackling safety issues at their origin.

2. Scientific and emerging evidence – a case for judicial value judgments

The first issue to address here is whether the court system is adequately equipped to face challenges as highly technical and scientific as those deriving from ‘toxic tort’ cases – in particular, pharmaceutical product liability litigation. The debate is a long-lasting one, but a few elements in support of courts’ adequacy for this purpose can be briefly summarised with a bird’s eye view of contentious issues in the American and European scenarios.

American scholars are divided for example on the appropriateness of jury trials involving highly regulated products (and medicines in particular), as lay persons are allegedly unfit to review scientific evidence. The concern is particularly focused on the alleged eagerness of juries to side with plaintiffs and award exorbitant punitive damages based more on sympathy for the victims than sound evidence (the major argument for

applying the doctrine of federal preemption to FDA-approved products).⁷⁷⁵

While the concern is understandable, it appears to be more of an abstract preoccupation than a concrete problem given that several studies suggest that juries are capable of evaluating complex evidence under proper judicial guidance.⁷⁷⁶ Such guidance should allow for decisions to be based on proper evidentiary grounds and not on some form of prejudice against corporate defendants – this is also suggested by studies on the even distribution of trial outcomes.⁷⁷⁷ Moreover, the alleged inclination of juries to indulge in punitive damages appears to be less frequent in product liability claims than is often argued. The trend in adjudication suggests that judgments involving significant punitive damages only really occur in the face of “egregious misbehaviour”⁷⁷⁸ – that is, the very purpose for which they were designed.⁷⁷⁹ As for the robustness of trial evidence, the

⁷⁷⁵ The literature on the topic is vast. We refer here in particular to the contributions of Owen D.G., “Dangers in Prescription Drugs: Filling a Private Law Gap in the Health Care debate”, *Connecticut Law Review*, 42, 2010; Owen D., *Products liability law*, 2nd ed., Hornbook Series, Thomson West Group, 2008; Sharkey C.M., “Federalism in Action: FDA Regulatory Preemption in Pharmaceutical Cases in State versus Federal Courts”, NYU School of Law, *Public Law & Legal Theory Research Paper Series*, n. 08-04, 2008; Sharkey C.M., “Preemption by Preamble: Federal Agencies and the Federalization of Tort Law”, *De Paul Law Review*, 56, 2007; Cranor C., *Toxic Torts – Science, Law and the Possibility of Justice*, Cambridge University Press, 2006; Struve C.T., “The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation”, *Yale Journal of Health Policy, Law & Ethics*, 2005; Viscusi W.K., *Regulation Through Litigation*, Brookings Institution Press, 2002; Jasanoff S., *Science at the Bar*, Harvard University Press, 1994.

⁷⁷⁶ This has been argued in particular by Sharkey C.M., “Federalism in Action: FDA Regulatory Preemption in Pharmaceutical Cases in State versus Federal Courts”; Sharkey C.M., “Preemption by Preamble: Federal Agencies and the Federalization of Tort Law”; Jasanoff S., *Science at the Bar*, p. 114 ff on “toxic torts and the politics of causation”; and Cranor C., *Toxic Torts*. In particular the ‘gatekeeping’ function of judges as provided by the Federal Rules of Evidence analysed in chapter VIII is a strong safeguard, to the extent that, according to Cranor, it might even be excessive in depriving juries of part of their fact-finding function. See for a recent contribution restating the general competence of jurors in assessing scientific evidence Hans V.P., Kaye D.H., et al., “Science in the Jury Box: Jurors’ Comprehension of Mitochondrial DNA Evidence”, *Law and Human Behavior* 35, 2011; and Diamond S.S., Salerno J.M., “Empirical Analysis of Juries in Tort Cases”, *Northwestern Law & Econ Research Paper* No. 12-19, available at <http://ssrn.com/abstract=2171938>.

⁷⁷⁷ On this point see in particular Struve C.T., “The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation”, p. 590 ff.; see also on a related point the trends in class action pre-trial certifications described by Klonoff R.H., “The Decline of Class Actions”, *Washington University Law Review* 90, 2013.

⁷⁷⁸ See Struve C.T., “The FDA and the Tort System”, p. 590; and see the study by Eisenberg T. et al., “Juries, Judges, and Punitive Damages: An Empirical Study”, *Cornell Law Review* 87, 2002, analysing in particular how punitive damages are normally awarded in cases of “intentional misconducts”; more recently the trend is confirmed by Diamond S.S., Salerno J.M., “Empirical Analysis of Juries in Tort Cases”.

⁷⁷⁹ On the function of punitive damages see among many others Posner R., *Economic Analysis of the Law*, Wolters Kluwer, 2007, p. 192 ff; and the contributions in Rabin R., *Perspectives on Tort Law*, ASPEN, 1995, and Schuck P.H. (ed.), *Tort Law and the Public Interest – Competition, Innovation and Consumer Welfare*, Norton, 1991.

demanding tests developed for the admissibility of scientific evidence, particularly in the most contentious forms of expert witnesses and reports, constitute a strong safeguard against the risk of ‘junk science’, or more to the point, actually biased evidence.⁷⁸⁰ In his essential contribution to the study of toxic tort litigation in America, Carl Cranor has persuasively argued that juries perform their duties to decide on the facts of complex cases in a generally competent manner,⁷⁸¹ with the safeguard that the trial system allows for judicial oversight and intervention when a jury decides in favour of one party “but a judge [finds] that no reasonable jury could come to such a conclusion”,⁷⁸² in which case juries’ verdicts can be overturned.

For the avoidance of doubt, this is not meant to be an argument in favour of jury trials *in general* – such an argument would require a study on its own and is too complex to be addressed here. This is simply, as suggested above, a ‘pointer’ to the fact that the American judicial system does possess structural antidotes to the risks of decisions tainted by incompetence or bias.

Aside from the specific context of jury trials, the adequacy question extends to courts in general, and judges in particular. Are judges equipped to confront highly technical and scientific matters? The question is a delicate one and has been the subject, again, of prolonged debates.⁷⁸³ A contribution that we propose here is that, facing uncertain evidentiary scenarios, courts seem to be adequately equipped to make the necessary value judgments required for decisions in specific cases. The complex judicial discussions regarding the appropriate criteria for establishing proof of causation (and specific causation in particular) are a testimony to the ability of courts to, first, engage with the subject, and, in time, self-educate towards better understandings of complex technical questions. The fascinating discussions of general versus specific causation provided by the UK Court of Appeal and Supreme Court on the one hand, and the US and Texas Supreme Courts on the other, are instructive examples of legal decision-making on the

⁷⁸⁰ See the discussion in chapter VIII on the *Daubert* trilogy of cases, *Daubert v. Merrell Dow Pharmaceuticals Inc.* 113 S. Ct. 125 L. Ed. 2d 469, 1993, *General Electric Co. v. Joiner* 118 S. Ct. 512 Ed 508, 1997, and *Kumho Tire Co v. Carmichael* 119 S Ct 1167, 1999.

⁷⁸¹ Cranor C., *Toxic Torts*, p. 70 ff on ‘Judge-Jury responsibilities’; and Jasanoff S., *Science at the Bar*, p. 114 ff.

⁷⁸² Cranor C., *Toxic Torts*, p. 42.

⁷⁸³ We refer to the literature suggested in the beginning of the chapter; the European perspective is considered in Goldberg R., *Medicinal Product Liability and Regulation*, Hart Publishing, 2013; Stapleton J., “Factual Causation, Mesothelioma and Statistical Validity”, *Law Quarterly Review* 128, 2012; Goldberg R. (ed.), *Perspectives on Causation*, Hart Publishing, 2011.

basis of controversial evidence.⁷⁸⁴ Interestingly, a major criticism directed especially to the Anglo-American courts in their evolving interpretation and use of epidemiological evidence highlights the ‘policy-like’ nature of these decisions (or to use the term adopted above, the value-based nature of the judgments).⁷⁸⁵ There is little doubt that this is the case. Courts do act as surrogates of policy makers when confronting cases permeated by scientific uncertainty. What is argued here is that, in the face of imperfect regulatory schemes contributing to the level of uncertainty beyond its unavoidable and systemic measure, this ‘surrogate’ role is essential.

The role of courts in evaluating and admitting evidence extends to complex decisions on development risk and emerging issues. The issue has been explored in chapter VIII, identifying a common theme in the Western judicial attitude leaning towards a strict interpretation of what is to be considered ‘reasonable access’ to scientific knowledge related to issues of emerging risk in liability assessments. This delicate exercise has been another field of judicial development with interesting convergences. *Wyeth v. Levine*⁷⁸⁶ has readjusted the tone in American product liability, with a decision that recognises the limits of the regulatory system and shifts the bulk of the responsibility of safety monitoring back into the manufacturer’s camp after a temporary exclusive reliance on the FDA’s role.⁷⁸⁷

As observed, this attitude is not dissimilar to the interpretation of development risk in the EU. This interpretation, in a legal framework free of a pure regulatory compliance defence, highlights the responsibility of the manufacturer in taking into account the highest levels of relevant scientific knowledge.⁷⁸⁸ The interpretation of what should be considered reasonably available shows a certain degree of variance across MSs,

⁷⁸⁴ See in chapter VIII the discussion of the cases *Sienkiewicz v Greif (UK) Ltd* [2009] EWCA 1159, [2010] QB 370, and [2011] UKSC 10, [2011] 2 AC 221; *Merrell Dow Pharmaceutical Inc. v. Havner* 953 SW 2d, Texas Supreme Court, 1997; *Merck & Co. Inc. v. Garza* 347 SW 3d, Texas Supreme Court, 2011; and the important contribution of the French caselaw on non-statistical evidence, Cassation Civile Arrêt n 605 9 Juillet 2009 08-11.073/2009, and the contentious Cassation Civile 26 Septembre 2012, 11-17.738/2012.

⁷⁸⁵ See in chapter VIII the discussion of the critiques of the ‘double risk’ theory raised by American commentators, in particular *Restatement (Third)* commentators: and see *comment c* to the *Restatement (Third) on Torts*, ALI, 2010.

⁷⁸⁶ *Wyeth v. Levine* 129 S. Ct. 1187, 2009.

⁷⁸⁷ See the extensive discussion of the doctrine of preemption applied to FDA-approved products in chapters VI and VII.

⁷⁸⁸ See the discussion in chapter VII of Case C-300/95 *Commission of the European Communities v. United Kingdom of Great Britain and Northern Ireland* ECR 1997, I-02649, and the related Opinion by Advocate General Tesaro.

as discussed in chapter VI.⁷⁸⁹ A common thread seems to emerge nonetheless in judgments from different legal contexts, stemming from the original ECJ decision in *Commission v. United Kingdom*.⁷⁹⁰ The concept of reasonable availability, overcoming the paradox of a liability assessment exclusively tied to pre-marketing assessment knowledge,⁷⁹¹ since its original ECJ construction, has been adopted and refined by national case law – we have referred to, for example, the UK case *A & Ors v. National Blood Authority*⁷⁹² in chapter VII. For the purposes of evaluating the competency of courts in managing litigation involving complex scientific evidence, another example from a different national experience is of use.

The Italian judiciary has throughout the 1990s and 2000s elaborated a concept of manufacturers' responsibility in relation to emerging relevant knowledge that runs in parallel with the European one, and, although based on a different legal framework, reaches converging conclusions. The leading case involves the bio-tech medicinal product Trilergan. The case involved a patient alleging liver intoxication (hepatitis B in the specific case) caused by use of Trilergan, the active ingredient of which is derived from human gamma-globulin.⁷⁹³ The reasoning of the Corte di Cassazione in interpreting article 2050 of the Italian Civil Code revolves around the responsibility of the manufacturer beyond his formal regulatory duties.⁷⁹⁴ The interesting element of this case is that while Trilergan had successfully complied with the safety requirements and passed the test methods for its blood component as prescribed by law, the producer Crinos S.P.A. was found to have failed to demonstrate compliance with its supervening 'duty of care'. In particular, what grounded the decision of the Court was the existence of an experimental test elaborated by an Italian university at the time the product was under review for marketing approval.⁷⁹⁵

⁷⁸⁹ In particular, significant special liability schemes such as the ones laid down in German law are anchored to stricter liability regimes.

⁷⁹⁰ Case C-300/95 *Commission of the European Communities v. United Kingdom of Great Britain and Northern Ireland* ECR 1997, I-02649.

⁷⁹¹ See the discussion in chapter VI and the argument as suggested by Cafaggi F., *The institutional framework of European Private Law*, Oxford University Press, p. 191 ff.

⁷⁹² *A and Others v. National Blood Authority* (2001) 3 All ER 289 (HC).

⁷⁹³ Trilergan was an anti-allergenic produced by the Italian company Crinos S.P.A., based on immunoglobulins imported from the US manufacturer Armour Pharmaceutical.

⁷⁹⁴ Article 2050 of the Italian Civil Code provides that "[w]homever harms others through an activity dangerous by its nature or by nature of the means employed to carry it out is liable to compensate the victims, if he does not prove to have taken all adequate measures to avoid the harm" (author's translation) – which introduces a duty of care beyond regulatory requirements.

⁷⁹⁵ On the judicial discussion of the experimental RIA method see Mattarelli R., Mezzini R., *Indennizzo e Risarcimento dei Danni da Prelievi e Trasfusione di Sangue*, Maggioli Editore, 2014, p. 204 ff;

The test was showing significant results at the time, and although not yet accepted by the general scientific community (and not yet enshrined in the required regulatory standards), the Court considered that it would have been reasonable to expect that the producer of a highly specialised product would be informed of the existence of new experimental techniques – in particular, the new testing methodology for identifying potential hepatotoxicity of composite medicinals derived from blood products.⁷⁹⁶ In interpreting article 2050, which requires the manufacturer to demonstrate taking all appropriate steps in order to avoid the risk of damage, the Court held Crinos liable for failure to fulfil its legal duty. The conclusive decision of the Corte di Cassazione,⁷⁹⁷ released around the same time as the *Commission v. United Kingdom* judgment, shows a substantial parallel with the idea of ‘availability’ developed by Advocate General Tesouro and adopted by the ECJ. This judicial interpretation has set the tone of Italian pharmaceutical product liability, and has been confirmed in subsequent cases.⁷⁹⁸

In 2012, the Tribunale di Sassari,⁷⁹⁹ in a judgment involving post-chemotherapy and odontological pharmacological treatments, confirmed the judicial idea of ‘availability’ while adopting the implementing legislation of the Product Liability Directive⁸⁰⁰ instead of the traditional article 2050.⁸⁰¹ The case involved a patient who suffered a severe ADR as a consequence of toxic interactions between the said two pharmacological treatments, as a result of which the patient decided to sue the manufacturer for failure to fulfil its precautionary duties. The Court observed that epidemiological evidence showed a statistically significant correlation between the post-chemotherapy treatment under

Bordon R., Rossi S., Tramontano L., *La Nuova Responsabilita' Civile – Causalita', Responsabilita' oggettiva*, Lavoro, UTET, 2010, p. 803 ff; and Cendon P., *Commentario al Codice Civile – Artt. 2043-2053: Fatti illeciti*, Giuffre', 2008, p. 822 ff.

⁷⁹⁶ Mattarelli R., Mezzini R., *Indennizzo e Risarcimento dei Danni*; and Bordon R., Rossi S., Tramontano L., *La Nuova Responsabilita' Civile*.

⁷⁹⁷ Cassazione Civile, 27 gennaio 1997, n. 814.

⁷⁹⁸ Bordon R., Rossi S., Tramontano L., *La Nuova Responsabilita' Civile*, p. 805; see also the fundamental discussion in Izzo U., *La Precauzione nella Responsabilita' Civile: Analisi di un COncetto sul Tema del Danno da Contagio per Via Trasfusionale*, CEDAM, 2004, and Recano P., *La responsabilita' civile da attivita' pericolose*, CEDAM, 2001, pp. 200-210.

⁷⁹⁹ Tribunale di Sassari, sentenza del 12 luglio 2012 (pending judgment by the Corte di Cassazione).

⁸⁰⁰ D.P.R. 24 maggio 1988, n. 224, *Responsabilita' per Danno da Prodotti Difettosi*.

⁸⁰¹ For a discussion on the disruptive effect of this decision see Bartolomeo J., “Pharmaceutical Company’s Liability for Injuries Caused by a Defective Drug: the New Trend in Italy”, *International Product Liability Review* 49, 2012: however, the decision as discussed in the text does not really contradict the previous decision (the case is currently being reviewed by the Italian Corte di Cassazione).

scrutiny and post-dental surgery treatment.⁸⁰² The Court however found in favour of the defendant on the basis that the specific ADR suffered by the patient in question had been only atypically defined at the time of the treatment.⁸⁰³ A solid definition of the ADR at stake and its statistical correlation to the post-chemotherapy treatment only emerged after the patient had undergone the treatment and therefore after the manufacturer could have acted upon the emerging knowledge – an interpretation of ‘reasonable’ availability which is arguably in line with the ECJ judgment and its national successors discussed above. The paucity and scarce circulation of the evidence at the relevant time, considered by the Court to be insufficient to hold the producer liable, differs substantially from the Trilergan situation involving a university-developed experimental test at a relatively advanced stage.

This brief summary of courts’ management of complex evidence suggests significant capacity within the judiciary to confront highly technical matters and strike balanced decisions with the available legal tools. While these decisions are certainly characterised by a degree of ‘policy-making’ (entailing value-based judgments), the argument here is that this should not be dismissed or criticised as overstepping, but rather welcomed as positive exogenous oversight of regulatory procedures. While the approval process is constructed on scientific evidence, regulatory outputs (both at the regulatory-design level and at the decision-making one) are very much based on what has been colourfully defined as “trans-science”⁸⁰⁴ – a discipline at the crossroads between pure science and policy involving decision-making on the basis of partial information, but more generally grounded on a “conventionally established” scientific basis, which is inherently different from a proven scientific truth.⁸⁰⁵ The brief overview presented here (and the observations made in chapter VII) suggests that courts have been shown to possess the ability of engaging and complementing the trans-scientific discourse, adding valuable external insights to an otherwise self-referential system.

⁸⁰² In particular, an epidemiological study suggested a correlation between the ADR in question of 25% in patients solely undergoing the post-chemotherapy treatment, and 75% in patients undergoing the combination of post-chemotherapy and post-dental surgery treatment, see *ibidem*.

⁸⁰³ *Ibidem*. The expert appointed by the Tribunale showed how the description of the ADR in question had only reached the scientific circle after the facts at hand.

⁸⁰⁴ The term is used by Jasanoff S., *Science at the Bar*, and first coined by Weinberg A., “Science and Trans-Science”, *Minerva* 10, 1972.

⁸⁰⁵ Whereas statements such as “under given circumstances water boils at 100° C” is scientifically sound insofar as it is controllable, verifiable, and replicable, a decision about the level of safety attributed to certain epidemiologic data is a value judgment (*based on a scientific observation, but interpreted in light of non-scientific factors*). For a comprehensive discussion of regulatory science see *ibidem*; Shapin S., *The Scientific Life*; and Jasanoff S., *Science and Public Reason*, Routledge, 2012.

3. Post-marketing judicial surveillance – a snapshot of timing, compensation, and regulatory value

The second possible criticism of the ability of courts to complement regulatory oversight of pharmaceutical safety relates to the inherent lengthiness and inefficiencies of litigation proceedings, which are comparatively ill-suited for a task that requires prompt remedial action in the face of emerging risks.⁸⁰⁶ The observations provided in chapters V, VII, and VIII seem however to contradict this assumption, as they show rather how administrative reactive measures suffer from structural delays, and in many cases are taken after litigation has been initiated (if not after its conclusion). The following pages offer a snapshot of the major cases analysed throughout the previous chapters in an attempt to highlight the timeliness of litigation reactivity compared to administrative action.

Vioxx – The timeline of administrative measures was discussed in chapter V. First approved in 1999, the drug underwent a series of labelling revisions after the VIGOR study showed an increase in the risk of cardiovascular ADRs, and was voluntarily withdrawn by the marketing authorisation holder Merck in September 2004 – after the subsequent APPROVe trial demonstrated that the statistical increase of cardiovascular events related to Vioxx use was significant. Litigation swiftly ensued (the first cases were filled in 2005 after the withdrawal),⁸⁰⁷ with varying outcomes, until the company decided in 2010 to settle aggregate claims for a total of roughly \$4.5 billion.⁸⁰⁸ A subsequent settlement followed in 2011 with 44 individual states to resolve pending civil disputes for a total of another \$950 million.⁸⁰⁹ The outcomes of litigation suggest that US victims were adequately compensated within a time span of five to six years from the withdrawal.⁸¹⁰ Since Vioxx has been on the European market for roughly the same period of time as the US, individual cases in Europe might be expected to have reached settlement, but no

⁸⁰⁶ In past years the case against litigation of product liability claims has been strongly made for example by Polinsky M., Shavell S., “The Uneasy Case for Product Liability”, *Harvard Law Review* 123, 2010; but see also the European debate on the preferability of alternative dispute resolution mechanisms to court litigation, referred to in chapter VIII.

⁸⁰⁷ *Rogers v. Merck* 6:2005 cv 02172 Alabama, 2005.

⁸⁰⁸ See the report by Drug Watch International, available at <http://www.drugwatch.com/vioxx/lawsuit/>.

⁸⁰⁹ See *ibidem*.

⁸¹⁰ See the discussion in Lahav A. D., “Rough Justice”, March 2, 2010, available at <http://ssrn.com/abstract=1562677>, suggesting that large settlements using statistical methods to compensate plaintiffs from the settled sum are currently the fairest method of compensation; but see also Erichson H., Zipursky B., ‘Consent versus Closure’, *Cornell Law Review* 96, 2011, suggesting that out of court settlements of this magnitude favour closure over consent of the plaintiffs (resulting in reduced compensation).

aggregate evidence to that effect is available.

In the Vioxx case, the litigation system had accordingly no visible impact on the specific regulatory process and only a compensatory function. It must however be noted that the case is rather exceptional insofar as it involves a voluntary withdrawal after less than five years of presence on the market. On the other hand, the subsequent regulatory reforms triggered by the saga have been discussed in chapter V.

Avandia – Again, we have illustrated the major steps in chapter V. As recalled, initial doubts about the cardiovascular safety of this anti-diabetes treatment led to different evaluations by the FDA and the EMA (who approved the product a year later on appeal by the manufacturer GSK). The turning point in the regulatory surveillance process was an independent meta-analysis published in June 2007.⁸¹¹ Following this event, the FDA and the EMA approved revised labelling containing ‘black-box’ warnings against the risk of cardiovascular ADRs. In 2010, subsequent reviews at the FDA prompted severe restrictions on the use of the drug, while the EMA opted for a suspension of the marketing authorisation. In 2010, and prior to both FDA and EMA final interventions, GSK was facing approximately 13,000 lawsuits in the US alone. The company reached a \$460 million settlement in July the same year to close about 10,000 cases.⁸¹² In 2012 GSK reached a further agreement with the US Department of Justice to settle charges relating to data withholding for about \$3 billion.⁸¹³ As for Vioxx, potential European lawsuits may have been settled individually, however numbers are not available. The Avandia timeline suggests that litigation and regulation proceeded at the same pace once relevant data were uncovered, with litigation producing a first major aggregate settlement three years after the start of proceedings and a final comprehensive one in 2012 – encompassing both Avandia and other alleged misbehaviour by GSK. We are unable to provide equivalent numbers for the European market, but it is worth noting how EMA’s suspension followed swiftly (September 2010) upon the first mass settlement.

⁸¹¹ See again Nissen S.E., Wolski K., “Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes”, *New England Journal of Medicine* 356, 2007.

⁸¹² See the report by Drug Watch International, available at <http://www.drugwatch.com/avandia/lawsuit.php>.

⁸¹³ See US Department of Justice, “GSK to Plead Guilty and Pay \$3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data”, Press release of 2 July 2012, available at <http://www.justice.gov/justice-news/>. This settlement covers misbehaviours related to a wider range of drugs including Paxil, see *infra*.

Paxil – The regulatory and litigation history of Avandia is inextricably linked to Paxil. While the direct outcomes of both the Vioxx and Avandia litigation were exclusively compensatory (the timeline suggests a *consecutio* between the first mass settlement in the US and the European suspension, but the material impact is unmeasurable), Paxil is interesting for two reasons. First, as recalled in chapter VII, the initial private lawsuit, successfully alleging failure to adequately warn for risk of violent and suicidal tendencies associated with withdrawal upon suspension of treatment, was a 2001 Wyoming case.⁸¹⁴ Here the FDA acted following the litigation outcome with the issue of a warning on severe withdrawal symptoms.⁸¹⁵ Secondly, chapter VII discussed extensively how, as a result of growing civil litigation relating to side-effects in juvenile populations under off-label Paxil treatment, the New York Attorney General launched a lawsuit immediately settled by GSK.⁸¹⁶ Beyond compensation, the regulatory outcome in this case was twofold – general and specific. At a general level the settlement required the compulsory publication of all trials for a ten-year period (which allowed for instance the decisive meta-analysis of Avandia in *NEJM*). As for the specific case, three months after the settlement the FDA released an internal review of clinical trials data confirming the increase of risk in suicidal tendencies in adolescent populations and resulting in label review.⁸¹⁷

Phenergan – The Phenergan case has been analysed for its regulatory implications. The initial lawsuit brought by Ms Levine on the adverse effects of intravenous methods of administration found her successful at both instances in the State of Vermont.⁸¹⁸ The interesting feature of the case, confirmed by the Supreme Court judgment discussed in chapters VII and VIII, is to be found in the ulterior requirement prescribed by the Vermont courts to adequately warn of risks related to the injectable version of the drug. The ramifications of the case for the US in terms of interactions between regulatory frameworks and litigation have been discussed. The impact on the specific case is also noteworthy. Following the Supreme Court judgment, in September 2009 the FDA imposed

⁸¹⁴ *Estates of Tobin Ex Rel. Tobin v. SmithKline*, 164 F. Supp. 2d 1278 (D. Wyo. 2001) – see the discussion in chapter VII.

⁸¹⁵ In December 2001: see the revised labelling available in the FDA ‘Drug Approval Package’, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2001/20-031S026_Paxil.cfm.

⁸¹⁶ *People of the State of New York v. GlaxoSmithKline*, filed in June 2, 2004 – case file available at <http://news.findlaw.com/wp/docs/glaxo/nyagglaxo60204cmp.pdf>, and see the discussion in chapter VII.

⁸¹⁷ See FDA, “Review and Evaluation of Clinical Data of SSRIs”, 16 August 2004, available at <http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4065b1-10-TAB08-Hammads-Review.pdf>.

⁸¹⁸ *Levine v. Wyeth* 944 A 2d 179, 184 Vermont, 2006 – see the discussion in chapter VII.

a ‘black box’ warning for all injectable forms of *Promethazine*.⁸¹⁹

Trilergan, *Genhevac*, *Levemir* – Although less spectacular than the multi-billion American settlements, European cases have proven capable of impacting the output of regulatory assessments, with litigation outcomes both supplementing and anticipating regulatory measures. As discussed above, *Trilergan* established the principle of a regulatory assessment to be adjusted and refined in light of the manufacturers’ superior knowledge of a highly technical field (a conception not dissimilar to that adopted by the Vermont court in *Wyeth* – that FDA assessments are a “floor and not a ceiling”).⁸²⁰ The case on the Hepatitis C vaccination in France⁸²¹ has been briefly mentioned in chapter VIII while addressing common tendencies in various judicial settings regarding the interpretation of specific causation. The French cases supplemented the original regulatory safety assessment by allowing individual reports and non-statistical evidence to establish a causal link between vaccination and a series of neurological disorders – even in the absence of supporting general epidemiological data. Finally, with the CJEU decision of 2014 confirming the validity of the German AMG in its amended version,⁸²² the German courts could require the manufacturer of *Levemir* to disclose all relevant information relative to the contested ADR – a beneficial result for the regulatory post-marketing surveillance regime, predominantly based on manufacturers’ disclosure.

The chapters dedicated to the judicial lens in pharmaceutical safety point at three interrelated conclusions. First, chapter VII suggests that courts do have an impact on data availability. They do so by either deciding cases or driving them to settlement, or with specific procedural decisions oriented at data disclosure. Second, chapter VIII discussed the intricacies of ‘toxic torts’ involving complex scientific evidence, in which it is much easier for the litigation system to be a *proxy* for participatory mechanisms in the presence of consolidated collective redress schemes (and in particular American class actions). Where these mechanisms are absent, the compensatory function of litigation is reduced, but the complementary regulatory function is preserved when cases do reach the courts.

⁸¹⁹ FDA, ‘FDA Requires Boxed Warning for Promethazine Hydrochloride Injection’, Press Release, 16 September 2009, available at <http://www.fda.gov/NewsEvents/Newsroom/>.

⁸²⁰ See above on the application of article 2050 Italian Civil Code – Cassazione Civile, 27 gennaio 1997, n. 814.

⁸²¹ See Cassation Civile Arrêt n 605 9 Juillet 2009 08-11.073/2009, involving the anti-hepatitis vaccine *Genhevac*, commercialized by Pasteur Aventis.

⁸²² Case 310/13, *Novo Nordisk Pharma GmbH v. S.*, ECR 2014: see the discussion in chapter VII.

Third, the brief recapping exposition in this chapter argues that courts can indeed be an adequate instrument of post-marketing oversight, as they can show relative competence in addressing complex trans-scientific matters, as well as a reaction time comparatively competitive with that of regulatory measures.

CHAPTER X

REASSEMBLING THE PUZZLE

THE DOUBLE CASE FOR JUDICIAL COMPLEMENTARY GOVERNANCE

This final chapter reassembles the puzzle towards the concluding argument in favour of an enhanced role of courts in complementing regulatory schemes of pharmaceutical safety. The material covered throughout eight substantive chapters is re-systematised here and confronted with the questions and hypothesis initially raised in chapter I. The first two sections accordingly assess the results of the analysis of the institutional design and of the judicial lens in pharmaceutical safety. On these premises, the third section will suggest that a judicial ‘hard look’ at regulatory processes can provide substantial assistance in enhancing consumer safety. The Introduction opened the floor for a debate as to whether problematic regulatory features, exacerbated by the increasing transnational development of standards and procedures, call for renewed in-depth surveillance from a perspective external to the regulatory system’s mechanisms. The conclusions emerging are as follows.

1. Closed regulatory systems and problematic outputs

After giving an overview of what we called different types of *rebus* in pharmaceutical regulation, the thesis developed an analysis of the regulatory architecture, referred to as ‘the institutional design’. The reconstruction in chapter II served the purpose of tracing the developmental path of pharmaceutical regulation in the two major markets which form the general investigative object of the thesis: the US and the EU. In light of the transnational developments of the last decades, the description of the institutional design also involved the ICH, as a crucial forum for guidelines and standard-setting.

What emerged from this first step was a progressive evolution of the major regulatory agencies throughout three successive phases. The first phase we have defined as the acquisition of an ever greater independence by agencies and what can be referred to as their internal ‘bodies of expertise’ *vis à vis* political institutions (both in the policy-making and in the decision-taking stages). The second phase, logically following the initial one, consisted of the creation and consolidation of a significant asymmetry between the formal distribution of power among political institutions and agencies, and the substantial exercise of said power – in particular with the consolidation of *de facto* decision-making power in the hands of specialised committees such as the CDER and the CHMP. While formally a great deal of decision and policy-making power remained within political institutions (for example with the Commission remaining the final decision-maker acting upon EMA’s advice), the actual exercise of power became fundamentally outsourced to agencies that have been organising that exercise independently. The third phase identified was the shift to the transnational space, where a dichotomy exists between the transnational nature of the regulatory process and the domestic design of the regulatory frameworks. The description of the ICH in the concluding section highlighted the peculiar nature of this transnational forum, the uncertain physiognomy of which questions its ability to introduce a reliable international regulatory structure.

The description of the institutional design and its progressive separation from the rest of the public sphere, coupled with the transnational shift, required a ‘questioning’ of three salient aspects. The first element, analysed in chapter III, involved the quality, provenance, and compatibility to receiving markets of scientific data resulting from outsourced clinical trials. The chapter started from the hypothetical premise that a dichotomy between domestically designed regulatory frameworks and transnational practices can create difficulties for the quality of safety and efficacy assessments. The argument suggests that strong domestic regulations can be vulnerable when permeated by exogenous factors that are not fully accounted for. In particular the concern lies in the effectiveness and the level of safety delivery that can be expected from a transnational practice shoehorned into domestic schemes. This chapter had to be constructed on the basis of aggregate numbers, as product-specific research was undermined by the substantial inaccessibility of essential data (an obstacle which the recent EU Regulation 536/2014 will possibly surmount, if only for future EU-based research). The results of the

chapter's analysis highlighted a preoccupying degree of uncertainty, specifically relating to four major factors: (1) structural deficiencies in third countries' data control quality, (2) divergences in therapeutic culture between testing and receiving markets, (3) ethical misconduct with scientific implications (especially from the ROW region), and (4) issues related to patient recruitment, treatment-naïvety, and genetic aspects of treatments' success or failure. The tentative conclusion reached was that since consensus on the phenomenon of out-sourcing trials is widespread among scientists and regulators, and consensus on the ambiguity of the quality of the resulting scientific data is broad within the scientific community, a concrete legal issue ensues regarding substantial compliance with requirements of safety and efficacy in the receiving markets. Coming back to the initial hypothesis laid down in chapter I, according to which the increasing number of bodies involved in the approval process of new medicines across the world generates non-negligible levels of uncertainty as to the quality of the emerging data, the findings of chapter III, while not conclusive, open the floor to a debate.

As argued in chapter I, the development of pharmaceutical regulation poses problems not only on the effectiveness but also on the legitimacy side. Thus, chapter IV shifted the focus of the 'questioning' to the provenance, law-making mechanisms, and sources of legitimacy of the rules governing regulatory practices, in particular as regards the acceptance of foreign data. The intent was to uncover the mechanisms through which strong but domestically oriented regulatory frameworks absorb external inputs. Following the recalled scheme of threefold regulatory evolution, the analysis was focused on the second and third evolutionary phases, namely the detachment of regulatory power from political oversight and the ensuing shift to the transnational arena, entailing a problematic dichotomy with the domestic nature of regulatory systems. The conclusions here were twofold. On the one hand, the analysis suggested that the mechanisms of alternative deliberative democracy, very much relied upon at the EU level and somewhat in the US, according to which decisions are reached (short of classic representative democracy mechanisms) via stakeholder consensus, are unfit for the transnational scenario led by the ICH. The carefully crafted EU procedural standards succumb in the ICH arena to a negotiating logic the process of which is hardly measurable. Facing substantial difficulties in shaping a legitimating mechanism at the rule-making stage, the alternative is an output-based legitimacy – based on the efficiency and efficacy of the policy results. The

concluding observation in this sense was focused on the duality of policy objectives typical of pharmaceutical regulation: facilitating marketability of products and ensuring end-user safety. The first limb of the policy commitment is consistently pursued by the regular implementation of regulatory guidelines oriented towards expedited and efficient marketing approval. As for the protection of health and safety, the materials analysed throughout the thesis suggest a measure of caution, and invite in-depth reflection on the consequences of clinical-trials outsourcing and resource limitations of monitoring agencies. The second hypothesis laid down in chapter I suggests that the ICH is upholding trade considerations as a primary goal, and achieving that goal through public-private negotiations where core choices on levels of risk exposure are negotiated. The discussed centrality acquired by ICH Guidelines such as the GCP or the SPCT for mutual recognition of clinical trials data seems to substantiate this hypothesis.

To put the institutional design to the test of safety delivery, chapter V offered an evaluation of safety outcomes through the analysis of a series of cases. The initial argument was that uncertainties of data quality and provenance, coupled with issues of legitimacy of the rule-making mechanisms and accountability of the rule-makers, could only be surmounted by the highest results in the achievement of legislative goals – and in particular, the achievement of consumer safety, in accordance with the general perspective of the thesis. To this end, the case studies were structured to question the quality of the pre-marketing approval process and the ability of the post-marketing surveillance mechanisms, as currently designed, to overcome issues of data uncertainty and to effectively react to emerging safety issues (a double requirement for the output of the regulatory system to overcome the ‘democratic deficit’ at the rule-making stage). The focus was therefore on safety outcomes interpreted as a sum of pre-marketing results and effectiveness of reactive measures. The results suggested, again, cautionary reflections. As recalled, a measure of uncertainty seems to permeate pre-marketing scrutiny because the provenance and reliability of data is being progressively (in parallel to the increasing transnationalisation of procedures) impacted by major complicating factors. The analysis of the safety output of regulatory mechanisms suggests that risk discovery is particularly difficult at the pre-marketing stage (again, the problematic features described in chapter III compound this difficulty –Vioxx for instance, despite the impossibility of pinpointing the location of pivotal trials, was admittedly tested transnationally). But more prominently,

what emerged is that post-marketing risk-discovery appears to be characterised by elements of fortuity that are more the product of imperfect regulatory mechanisms than of unavoidable scientific hazard, while the reactions of the regulatory system can prove to be slow and ineffective. An ulterior complicating factor is the lack of sufficient resources at the agencies' disposal to perform their inspection duties both pre- and post-marketing.

A fundamental question raised in chapter I was: *to what extent is procedure affecting substance?* In light of the institutional design's analysis, the answer is threefold. First, it seems that procedure affects the quality of scientific data insofar as multi-local testing raises fundamental safety questions yet to be comprehensively addressed by regulatory mechanisms (chapter III). Second, the shift to the transnational arena has transformed procedurally standardised decision-making mechanisms into a negotiation process, the proceedings of which are not fully accounted for (chapter IV). Third, post-marketing mechanisms run the risk of serious lapses in the delivery of effective safety control, which risk is at least in part a function of their insufficient funding structures (chapter V). These problematic aspects of post-marketing surveillance, independent *per se* from the transnational procedures, can be aggravated by the increased pre-marketing uncertainty resulting from the analysis provided in the first part of the thesis.

A further question suggested in chapter I was to the effect: *are we not asking too much from regulation under the current circumstances?* The four chapters dedicated to the institutional design of pharmaceutical regulation provided a series of pointers corroborating the argument that the regulatory system cannot be self-sufficient in the pursuit of consumer safety. The subsequent part of the thesis shifted the focus to the ability of courts to constitute the necessary exogenous complement to open up and assist the otherwise *closed* system, as initially described and emerging from the analysis of regulatory design.

2. Technical complexity and fundamental choices – The easy case for judicial complementarity

Analysing the lens of the judiciary in pharmaceutical safety entailed a complex and multi-layered study of a number of defining features of liability rules and court processes. To argue for courts as the fit and necessary agent to open the *closed* system, the opening chapter VI began from the observation that the most prominent role of courts in

pharmaceutical cases is to adjudicate tort claims. The analysis therefore focused on the development of liability rules in the US and the EU as applied to pharmaceutical product liability cases. The focus was on specific aspects of those rules, subsequently deepened in the following chapters: the ideas of foreseeability of risk, availability of knowledge, and regulatory compliance, all closely linked with the regulatory framework previously analysed. The resulting overview was relatively fragmented at first sight, with legal and interpretative divergence between the US and the EU as well as within the EU. Generally, the overview suggested a very case-specific identification of the issues to be adjudicated (with concurrence of compensatory and deterrent goals in different proportions depending on the legal setting in question). That notwithstanding, the brief analysis of product liability rules seemed to open the door to the potential for judges to question the origin of a defective product, and in particular, looking beyond traditional tort adjudication, whether the cause of a harmful defect could be a flaw in the regulation allowing for low-quality pre-marketing assessment. That is the idea underpinning a ‘hard look’ doctrine, suggested throughout the thesis and expanded in the final sections of the chapter.

The paradigm needed to be tested, and with a sequence of three brief chapters, the thesis proceeded to address three fundamental questions raised in chapter I, somewhat mirroring the analysis undertaken for the institutional design.

The first question was the following. *Can courts play a role in the management of pharmaceutical products in terms of introducing transparency and coherence as regards the quality, relevance, and nature of scientific knowledge? In other words, can courts go beyond pure cost-benefit assessments, deferential to regulatory decisions, and enter the realm of uncertainty with value-based judgments?*

Chapter VII addressed the matter. The results of the study were composite. The analysis of case law provided in two sections suggested that, through judicial intervention, scientific evidence that gets lost or withheld in the regulatory process can be uncovered and integrated in specific risk assessments, or made generally available for more diverse purposes – this was particularly evident in the GlaxoSmithKline Paxil settlement leading to temporary full data disclosure. The ability to authoritatively impose full disclosure of information enables courts to effectively supplement regulatory agencies’ data pools, overcoming structural difficulties encountered by regulators in accessing essential

information (which while necessarily limited on pre-marketing assessment, appears to be unnecessarily uncertain, and equally so at the post-marketing stage as a result of imperfect surveillance mechanisms, as discussed above). Going beyond liability cases, the chapter showed how imposing disclosure can influence the regulatory system at large (with access to information guaranteed beyond the facts of a single case, and even the potential to influence forthcoming legislation).

Beyond the capacity of individual court decisions to directly influence accessibility of data, the analysis moved to related issues of knowledge availability, going back to the field of product litigation. What emerged was interesting. The chapter concluded with an observation that while the attitudes of US and EU courts towards access to and inclusion of relevant scientific knowledge in liability assessments have developed through time independently and in adjacent rather than juxtaposing fields, the results are not dissimilar. There is a common theme identifiable in the fact that both judiciaries seem to share a significant level of awareness as regards the flaws of the regulatory framework – an awareness that appears to cover the limited data grounding pre-market approvals as much as the shortcomings of post-marketing surveillance. This awareness seems however counterbalanced by a generally deferential approach to regulatory findings – with compliance still considered at least *prima facie* strong evidence of safety – which typically restrains courts from questioning the origin of emerging safety issues (potentially the regulatory architecture itself) and confines their enquiry instead exclusively to specific conduct. The positive attitudes shared by American and European judiciaries towards inclusion of relevant knowledge in liability assessments does warrant the conclusion that the ‘keys’ to open the *closed* system are in place. The question reproduced above asked whether courts can impact the quality of scientific knowledge. The analysis suggests that they certainly can impact the *availability* of knowledge and its inclusion in the assessment of safety – thus indirectly improving the quality of the assessment itself. The discussion over the various judicial debates also highlighted a judicial inclination towards entering *the realm of uncertainty with value-based judgments*. This inclination emerged in the following chapters too.

The second question raised in chapter I on the potential role of courts inquired: *can courts act as a democratic agent? Can they act as a proxy for participatory democracy which appears to be lacking at a transnational level through accessible national enforcement mechanisms?*

This was a particularly complicated issue to tackle. To provide a meaningful answer the structure of chapter VIII had to be multi-faceted. In particular, the issue of accessibility of courts (a premise to evaluate their ability to act as a ‘proxy’ for participatory democracy) was divided into two major aspects. The first, proof of causation in liability litigation, is an integral part of accessibility as proving a causal link in a field very much characterised by scientific uncertainty is a formidable obstacle for any litigant. The analysis suggested an encouraging picture, showing the versatility of judges and their ability to confront highly technical material in making fundamental choices about the elements of causation – which contributes to answering the first question raised above on the ability of judges to engage uncertainty with value-based judgments. The scene depicted, again composite and with degrees of variations across different legal orders, allows for the identification of a common thread. General statistics emerging from epidemiological studies are more and more relied upon, with the caveat that non-statistical and individual elements can or have to be taken into account depending on the facts at hand. While proof of specific causation remains the heaviest burden on plaintiffs in product liability cases involving medicines, the judicial interpretation appears to be both generally reasonable and evolving over time, suggesting progressively incremental know-how in handling complex evidence.

The second and related aspect took up the broader point that aggregate litigation, and in particular the American model of class actions, seems better suited than individual cases to guarantee widespread accessibility of court processes. In particular, the aggregation of individuals sharing a given factual *commonality* contributes from the pre-trial phase to building the evidentiary foundations of both general and specific causation. Absent similar mechanisms in the EU, access to justice maintains its causal difficulties and requires more individual initiative. The impression is however that once cases reach the EU courts they do have an impact, as the analysis in both chapters VII and VIII uncovered.

The answer to the question on the ability of courts to act as a proxy for participatory democracy is, then, necessarily multi-layered. The first point is that the US court system appears to be still better equipped than its EU counterparts in allowing diffuse accessibility. A debate is in motion in the EU, and it will be interesting to evaluate what kind of collective redress mechanisms (applicable to our field of interest) may be

devised. A second point relates to an issue identified within the question: can courts be expected to act as a proxy for participatory democracy through national enforcement mechanisms? Two observations are necessary. On the one hand, access to justice is a desirable goal because of the direct compensatory effect of court decisions – and here is where any obstacles to individual participation in litigation are problematic. On the other hand, in terms of exercising a form of quality control over regulatory processes (a bottom-up ‘relocation’ of public control, as suggested in chapter I and later in this section), arguably even a handful of cases may be sufficient. The analysis has shown how, when cases do reach courts, they are competently discussed with significant repercussions. It appears that in this case, the answer to the initial question has to be ambivalent and requires further development in the third section of this chapter.

The final question raised in chapter I tackles the issue of safety delivery: *what are the opportunities for courts to deliver consumer safety (and if so, to go beyond the specific case and influence the policy-making, which entails a broad understanding of the concept of ‘regulatory compliance’)?* This question had already received a positive but partial answer in chapters VII and VIII. In tackling both critical topics of knowledge availability and causation, courts have shown an ability to implicitly or explicitly engage with the regulatory framework. Chapter IX provided elements pointing at a significant capacity of courts to manage complex issues and, in particular, trans-scientific issues involving a delicate balance between scientific evidence and core value choices. The idea of ‘regulatory compliance’ has been interpreted, for example, as a minimum threshold necessarily complemented, when required, by further duties of care. The quality and depth of the judicial debate on matters relating to the nature, reliability (leaning towards the ‘policy side’ of the mix, without unduly intruding into the realm of pure scientific intricacies), and accessibility of scientific evidence, and the responsibility of the manufacturer therefor, corroborates the claim that courts are adequate venues for the review of regulatory assessments very much based on trans- or regulatory science. On the ability to deliver consumer safety, the selection of cases suggests therefore a positive case-specific answer, while the analysis summarised above also showed how courts’ decisions have the potential to impact the regulatory framework. That impact seems however still very much episodic, and while judges show a significant degree of awareness of regulatory flaws, this tends to be translated into case-specific

reactive decisions, with regulatory impact beyond the single case happening more through fortuitous small-scale domino effects than systematic reviews.

What emerged from the overall analysis allows for a preliminary conclusion, the contours of which have been traced throughout the four chapters dedicated to the judiciary. This is what we refer to in this section's title as the 'easy case' for judicial complementarity. The idea of an 'easy case' is borrowed from John Goldberg and Benjamin Zipursky⁸²³ in their effective rebuttal of Mitchel Polinsky and Steven Shavell's "Uneasy Case for Product Liability".⁸²⁴ The argument of Goldberg and Zipursky revolves around how doing away with product liability is unsatisfying in terms of tort's deterrent and compensatory functions and victims' welfare. In particular, the key to the argument developed throughout the piece is the incremental nature of the benefits brought by product liability litigation as regards consumer protection, wrongdoing deterrence, equality before the law, and the necessary reinforcement of general "norms of responsibility".⁸²⁵ What can we add in light of our analysis? As suggested in chapters VII to IX, the incremental value is more subtle than the here-and-now, going at times beyond the specificity of the case at hand. For instance, leaving aside the obvious example of disclosure orders that directly facilitate the discovery of unrelated harms (the GlaxoSmithKline Paxil settlement), a sequence of cases may generate positive incremental judicial know-how relating to complex technical matters, which has the merit of progressively refining judicial understandings of trans-scientific issues (as we have observed regarding admissibility and accessibility of evidence and proof of causation). The easy case for judicial complementarity seems also to involve the notion of "relocation"⁸²⁶ of the state's control to the post-factum monitoring phase, in a field characterised by detachment between regulatory bodies from public circuits and the move to the transnational sphere.

Still, there is room to argue that the full potential for judicial complementarity in pharmaceutical regulation has yet to be reached. Courts have yet to fully develop what we

⁸²³ Goldberg J.C.P., Zipursky B.C., "The Easy Case for Product Liability Law: A Response to Professors Polinsky and Shavell", *Harvard Law Review* 123, 2010.

⁸²⁴ Polinsky M., Shavell S., "The Uneasy Case for Product Liability", *Harvard Law Review* 123, 2010.

⁸²⁵ Goldberg J.C.P., Zipursky B.C., "The Easy Case for Product Liability Law", p. 1948.

⁸²⁶ To use again Saskia Sassen's terminology in Sassen S., "Immigration Policy in a Global Economy", 17 *SAIS Review* 2, 1997, and the wider analysis in Sassen S., *Territory Authority and Rights – From Medieval to Global Assemblages*, Princeton University Press, 2006.

have referred to as a ‘pedagogical’ function *vis à vis* the regulatory system towards the improvement of safety assessments – a role that would also refine the relocation of the state into a more comprehensive, less case-specifically reactive space. The argument, suggested in chapter I and referred to throughout the thesis in the analysis of existing legal tools (or ‘keys’) to open up the system, is now to be finalised in the following section. The crucial point is the notion of ‘deference’. What emerged from the analysis of the judicial role in pharmaceutical safety is that the courts’ interventions are mostly interpreted as an incremental factor ‘topping up’ regulatory safety assessments otherwise deferred to as proof of safety. The argument here is that a ‘hard look’ could be better suited to investigate the origins of problems rather than simply reacting to their unfolding – thus not only opening up the *closed* system, but also breaking the circle of *self-perpetuation*. This is the ‘complex case’ entailing an answer to the question raised in the opening chapter: *are we asking judges the right questions?*

3. A lesson from the past with an eye to the future – The complex case for a pedagogical role of courts

The complex case for judicial complementarity draws upon an old theory elaborated by the American judiciary between the 1970s and 1980s, the ‘hard look’ doctrine. Sheila Jasanoff effectively describes the evolution of judicial oversight of agencies’ decision and policy-making activity.⁸²⁷ The ‘hard look’ doctrine emerged as a means for judges to monitor agencies at a time when health and safety regulation was still in its early stages. A judicial ‘hard look’ involved not only a review of the scientific arguments and evidence grounding an agency’s decisions, but also the “agency’s procedural choices” in order to ascertain that “all relevant issues had been thoroughly aired, and that experts holding different viewpoints had been given an opportunity to participate”.⁸²⁸ The doctrine was a rough one and gave rise to alternating results, running the undoubted risk at times of unsound decisions based on anecdotal grounds, especially when courts ventured into substituting themselves for risk assessors.⁸²⁹ The recognised merit of the theory lies however in its ability to open up “a bureaucratic-technical culture that [operated], for the

⁸²⁷ Jasanoff S., *Science at the Bar: law, science and technology in America*, Harvard University Press paperback edition, 1997, pp. 69-92.

⁸²⁸ *Ibidem*, p. 77.

⁸²⁹ *Ibidem*, p. 82 ff.

most part, out of the public eye”.⁸³⁰ Specifically, what the judiciary managed to achieve, through a decade and a half of ‘hard looks’ at regulatory outcomes, was enhancing the regulators’ duty to make their decisions clear and understandable to a non-expert public, with rational explanations of the use of data and contentious scientific issues addressed thoroughly and accessibly – in this sense, courts ‘educated’ the emerging regulators on their public role which resulted in a “democratization of technical decision-making”.⁸³¹ The doctrine was subsequently abandoned in the mid-1980s when the political discourse shifted towards deregulation and, to reduce the burden of thorough reviews, courts began to embrace a deferential attitude to regulatory assessments involving complex expertise.

What is the potential lesson here? The complex case for a renewed pedagogical role of courts in enhancing pharmaceutical safety requires consideration of the ‘hard look’ idea in light of the results of the thesis summarised above. In particular, the question is what a ‘hard look’ in liability litigation could bring in terms of enhancing effectiveness and improving legitimacy of the regulatory system. The answer requires reflection on the issues described in the first part of the thesis dedicated to institutional design. We observed in chapter II a detachment of emerging pharmaceutical regulators from the rest of the public sphere. This is the phase during which, in the US, courts developed the ‘hard look’ – to educate inexperienced regulators on fundamental principles of accountability for their decision-making process and its outputs. The following shift, represented by the dichotomy between the national and the transnational sphere, in which regulators from consolidated frameworks negotiate the contents of new regulatory measures among themselves and with industry representatives, represents another novel phase in which regulators can benefit from a ‘re-educational’ judicial role. The magnitude of the phenomenon, namely the steady growth of transnational regulatory steps (especially clinical trials) in approval procedures (entailing growing reliance of domestic regulatory systems on transnational data, with its baggage of uncertainties), calls for scrutiny of the various problematic aspects analysed throughout the thesis (in particular in chapters III and IV), which are yet to be fully grasped by domestic regulators. While general judicial

⁸³⁰ *Ibidem*, p. 75.

⁸³¹ *Ibidem*, p. 92.

trends seem to vindicate an incremental role for judicial control⁸³² – adding ulterior elements to regulatory compliance, the ‘easy case’ – a pedagogical take (a ‘hard look’) could uncover to what extent the criticalities facing pharmaceutical regulation are unavoidable or if they are in part a direct product of standards and standard-setting mechanisms. In other words, a ‘hard look’ could address the origin of the problem – if the institutional design is indeed where a particular problem arises.

The democratisation of technical discourse, achieved in the US through some fifteen years of hard judicial scrutiny, is needed again for a non-dissimilar democratisation of the transnational technical discourse, entrenched in inaccessible negotiating mechanisms – to open up the *closed* system. Abandoning the deferential approach whereby regulatory compliance is proof (strong though not conclusive) of a product’s safety, and thereby engaging the regulators with the criticalities of the approval mechanisms (with their transnational complications), could also be the tool to break the circle of *self-perpetuation* – in this sense, giving a positive answer to the question raised in chapter I and above on the ability of courts to contribute to the legitimacy of this transnational regulatory architecture. The judicial tools elaborated by both American and European judiciaries, described throughout chapters VI to IX, seem fit to take up the challenge.

Suggested in chapter I, and corroborated by the subsequent analysis, the evolution of the state from rule-maker to rule-taker in pharmaceutical regulation has been accompanied by a form of ‘relocation’ of its authority to *ex post* judicial controls (with the significant exception of post-crisis legislative reactions, as discussed in chapter V). If the *locus auctoritatis* of pharmaceutical regulation is somewhat difficult to grasp in the current transnational setting, a ‘hard look’ at regulatory outputs, together with the beneficial impacts suggested above, could represent the completion of this relocation, whereby authority over unrefined regulatory practices can be regained through judicial oversight. It appears then that the responsiveness of courts to private claims, one of the most traditional features of nation states, is already performing, though with notable margins for improvement, a form of public oversight of an otherwise hardly challengeable regulatory system, now gone transnational. In Ulrich Beck’s words, judicial authority

⁸³² As discussed throughout, but see again the essential contributions by Kelemen R.D., *Eurolegalism*, Harvard University Press, 2011; and Coffee J. Jr, *Entrepreneurial Litigation – Its Rise Fall and Future*, Harvard University Press, 2015.

constitutes a “counter-power” in this global age,⁸³³ yet to fulfil its true potential.

4. A concluding remark

The results of this study are admittedly not conclusive in a number of aspects. They rather raise a series of unanswered questions that could be the object of future research endeavours. For instance, when discussing the institutional architecture of pharmaceutical safety and its dynamics, a recurring element encountered in the materials analysed and the ensuing draft of this work is the strong trade-oriented drive of regulatory cooperation initiatives. The need for reducing costs and easing regulatory burdens is continuously restated – from the early stages of the 1989 ICDRA conference, to the ICH’s foundation and subsequent activity, all the way to the current debates on T’TIP agreements. Questions arise due to the particular nature of the transnational regulatory networking device in place in this specific field. Is the trade necessity of unimpeded market access for pharmaceutical products overriding health and safety concerns? In other words, are the rule-makers unduly susceptible to corporate influences? If so, how much of an impact is the parallel lack of participation of civil society having on the quality of standards adopted? And beyond this, the question could be: is there evidence of a conscious shift towards sub-standard practices to ensure marketability and what would incentivise (or de-incentivise) such a shift?

These aspects deserve further digging in the future. Parallel fields of risk regulation suggest that industry can, on the contrary, be strongly invested in the promotion of high safety standards. A specific example is the regulation of food safety (in particular in the EU). While this is not the place to go into the details of this area of safety regulation, an observation can be made that private certification mechanisms, developed and implemented by the food industry itself, complement international and domestic legislation to the extent that they form an integral (and at times a dominant) feature of the governance mechanism ensuring health protection. Naturally, the parallels with pharmaceutical safety cannot be taken for granted, and neither can the conclusions drawn from food regulation be transplanted *tout court* to the pharmaceutical field – for a number of reasons that touch upon differences in the legislative and institutional framework at

⁸³³ Beck U., *Power in the Global Age*, Polity, 2005.

both national(s) and international levels, and differences in the shape of the two markets. Yet, the example suggests a measure of caution in evaluating the direct involvement of industry in regulatory schemes. The materials collated in this thesis are insufficient to support conclusive arguments one way or the other. That was not the *raison d'être* of this study.

The initial curiosity inspiring the genesis and development of this project derives from the simple observation that pharmaceutical injuries, despite the construction of the most extensive regulatory oversight mechanisms conceived for any product specific area, keep occurring. In particular, the analysis has shown that major, widespread harms materialise on a relatively cyclical basis, occasionally triggering legislative reactions. The discussion of the effects of regulatory compliance in liability cases further suggests that routine harmful events keep occurring and represent a significant social cost in terms of individual injuries and impact on healthcare systems. Why is that so? Is this simply inherent to the nature of pharmaceutical products, and therefore unavoidable, or is there room for improvement? This, in essence, is what the thesis tried to confront.

The description of problematic features in the institutional design, its progressive evolution, and subsequent transnational development opens a significant space for a debate in legal scholarship. The questions raised above in this section, concerning the possible existence of bias in the rule-makers, should be rephrased. If the regulatory mechanisms as they stand do show a concerning degree of uncertainty and fallibility, what we should really ask (above and beyond a quest for culpability) is: can we do better? There is no single or clear-cut solution to the challenging task of improving the protection of health and safety in a field involving unavoidably dangerous products – claiming otherwise would expose one to the risk of over-simplification, which is not only a scientific sin but more prominently an unrealistic foundation for remedial action. The intent of this thesis was rather to point to a set of existing legal tools, one that doesn't require profound reform or imaginative institutional restructuring, but has already demonstrated an ability to complement governance in uncertainty-ridden cases. Admittedly, the thesis very much limited its focus to the selected complementary instrument: courts. This was an explicit choice dictated by the conviction that external monitoring is key to a stronger regulatory architecture.

We do not contend that ‘doing better’ in pharmaceutical safety depends exclusively upon heavier reliance on courts. The problems exposed throughout the thesis, however, do deserve attentive discussion in legal scholarship, while the judicial tools analysed confirm the basic capacity of courts to address (at least in part) fundamental criticalities. The key argument of this work – a pedagogical role for courts, an argument *ad adiuvandum* rather than *contra* – is worth debating. The floor is open.

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